

**The epidemiology of brain
arteriovenous malformations in adults**

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Preface

Inevitably, clinical practice first aroused my interest in arteriovenous malformations (AVMs) of the brain. As a senior house officer in neurology, I strove to control a flurry of seizures – which were followed by hemiplegia – in a man of my own age, already wheelchair-bound by a prior haemorrhage from his brain AVM. I tried to determine whether he had suffered a recurrent haemorrhage, and if I suspected so, whether I should transfer him across London for urgent CT of the brain. I wondered what his prognosis might be. Should he be treated if this was a bleed, and if so, with which of the many available treatments?

At this time during my training, I was also developing a keen interest in clinical epidemiology, not only through my reading, but also by attending the Edinburgh Clinical Trials Course in 1996 and meetings about the new religion of evidence-based medicine. I was left believing that to address the most important unanswered clinical questions about the most common diseases was the priority, and that this could only be done using appropriate, robust research methods.

The next logical step seemed to be to combine my clinical and research interests. My attendance at the Edinburgh Clinical Trials Course and knowledge of the work of Charles Warlow's stroke research group led me to approach him about setting up a research project. Correspondence and a trip to Edinburgh left me with a one-page handwritten guide to grant proposals and the idea for the research projects that constitute this thesis! Whilst Charles Warlow gathered a multidisciplinary Steering Committee to facilitate these projects, I wrote grant applications with his help.

I was fortunate to be awarded a Medical Research Council Clinical Training Fellowship (which funded me through this thesis) as well as a project grant from the Chief Scientist Office of the Scottish Executive Health Department (which funded secretarial and programming support, as well as equipment and consumables).

This enabled me to start postgraduate study on 1 September 1998 and to continue until April 2002. Therefore, excluding a 3-month period when I undertook a clinical neurology locum, I was a member of staff at the University of Edinburgh for 3 years and 3 months. During this time my involvement was part-time in view of a weekly general neurology outpatient clinic, a regular out-of-hours on-call commitment, and

other distractions such as gaining ethical approval for the projects (Chapter 16), defending their conduct in the light of developments in data protection law and confidentiality guidance (Chapter 17), and applying for two further project grants to continue the research.

This thesis is organised into seven sections. The first comprises background information about brain AVMs and the systematic literature review that underlies the need for a prospective, population-based study of their frequency and prognosis. Such a project – the Scottish Intracranial Vascular Malformation Study (SIVMS) – forms the bulk of this thesis; its design, methods and definitions (both clinical and radiological) are described in the second section. Section 3 is devoted to an evaluation of these methods, and also includes a separate study of observer agreement in the radiological assessment of brain AVMs, because it is pertinent to the methods of SIVMS. The fourth section describes the main results of SIVMS (the incidence and presenting features of adults with brain AVMs in the first two years of the study), and a separate, but complementary study of the point prevalence of brain AVMs in just one part of Scotland. Following my conclusions in the fifth section, as a postscript I reflect on how difficult it was to gain ethical approval for these projects. Each chapter is organised in a standard format, with its main findings followed by a summary, followed by a discussion, followed by its tables and then its figures. The summaries of each chapter are collated in a summary of summaries (15.1, page 286) followed by my conclusions, and references are compiled in a single bibliography (Chapter 18, page 325).

This thesis was achieved by working as part of a team. I was responsible for searching and appraising the literature for the systematic review, with supervision from Charles Warlow. For the set-up and conduct of all the other research projects, I had administrative assistance from a part-time secretary and various sources of computing support (primarily a Napier University computing studies BSc student, but also Edinburgh University computing services and our departmental programmers). Whilst I was largely responsible for data modelling, structure, and fundamental table, query and report design for the research projects' databases, the complexities of turning the databases into tailor-made applications using programming languages were all attributable to computer programmers. Two Special Study Module medical students at the University of Edinburgh helped with the prevalence and observer agreement studies.

I supervised the work of the secretary, programmers and medical students, and collectively we were supervised on a weekly basis by Charles Warlow. Nationwide ongoing collaboration with SIVMS was facilitated by the Steering Committee, who met every 6 months to monitor the study's progress. The two neuroradiologists on the Steering Committee reviewed all the diagnostic imaging with me. I analysed the results, with some help from the departmental statistician with the prevalence and observer agreement studies. Although this thesis depended on teamwork, the responsibility for any errors herein is mine.

Acknowledgements

I now realise that a collaborative medical research project is not successful when its execution is easy, but simply when it works. Were it not for the involvement of several people, acknowledged below, my research might well have failed. I am also tempted to acknowledge those who hindered the progress of my research, for the intellectual stimulation they sometimes caused, which ultimately spurred me on to learn, study and publish more than I would otherwise have done.

My first debt is to the participants themselves, for their altruism in being willing to further knowledge about their condition. I am also grateful to the study's steering committee and collaborators (listed in the appendix) for their willingness to contribute participants and/or co-operate with data collection. Equal thanks are due to many general practitioners who helped in the same way. Without Rosemary Anderson's cheerful attitude and dependable administrative abilities, the study would almost certainly have failed. David Watson came to my rescue with his unique programming abilities and methods, by harnessing the power of Microsoft Access to automate almost every aspect of the study, thereby simplifying Rosemary's job and mine. There are many others who deserve thanks, including James Boyd and Lena Henderson at the Information and Statistics Division, Jason Fang and Nandita Pal (University of Edinburgh Special Study Module students), Estela Dukan (assistant at the library of Royal College of Physicians of Edinburgh), Tricia Gwynne-Jones (Chelsea and Westminster Hospital library), and Claire Leach and her colleagues at the Western General Hospital medical library. The observer variability study would have been impossible were it not for the candid participation of five busy interventional neuroradiologists: Andy Clifton, Andy Molyneux, Anil Gholkar, Shawn Halpin and John Millar. The whole of this thesis has benefited from the enthusiastic scrutiny of the Stroke Research Group and other contemporaries of mine in 'D block' at the Department of Clinical Neurosciences.

I never anticipated that postgraduate study would teach me as much about myself as about brain AVMs. My supervisor, Charles Warlow, helped me with both. Above all, he taught me to distinguish what's important from what's not. He was constantly supportive, retained a calming presence at the helm when the study entered stormy seas,

and frequently reminded me that, “good research is never easy to do.” I was grateful that his supervision was permissive, because it allowed me to follow my own reasoning, as well as make my own mistakes. He avidly corrected and enhanced my punctuation – especially teaching me the value of hyphenated asides mid-sentence – and he improved my writing style. Both of us being keen collectors of the “grocer’s apostrophe”, I was relieved that he never found any of mine to be misplaced. For all of this, and the time he has invested in me, I shall always be grateful.

Above all, for tolerating my protracted efforts to complete this thesis (and sometimes curtailing them), for their love, support and encouragement, I thank my parents and Anna. I dedicate this thesis to them.

Declaration

I declare that this thesis is of my own composition, and that the research contained herein is my own original work. None of this work has been submitted in support of an application for any other degree or professional qualification.

Rustam Al-Shahi

30 May 2005

Awards enabling and resulting from this thesis

1. MRC clinical training fellowship

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2. Chief Scientist Office, Scottish Executive Health Department, Project Grant

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Publications and presentations arising from work associated with this thesis

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Original papers

1. Al-Shahi R, Bhattacharya JJ, Currie DC, Papanastassiou V, Ritchie VR, Roberts RC, Sellar RJ, Warlow CP, for the SIVMS collaborators. Prospective, population-based detection of intracranial vascular malformations in adults: the Scottish Intracranial Vascular Malformation Study (SIVMS). *Stroke* 2003;34:1163-69
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2. Al-Shahi R, Pal N, Lewis SC, Bhattacharya JJ, Sellar RJ, Warlow CP and the AVM observer agreement study group. How much do neuroradiologists agree in their assessment of angiograms of arteriovenous malformations of the brain? Implications for management. *J Neurol Neurosurg Psychiatry* 2002;73:222
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2. Al-Shahi R, Bhattacharya JJ, Currie DG, Papanastassiou V, Ritchie V, Roberts RC, Sellar RJ, Warlow CP, SIVMS collaborators. The Scottish Intracranial Vascular Malformation Study (SIVMS).
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Invited lectures

1. *Brain arteriovenous malformations*, Royal Victoria Hospital, Belfast, Northern Ireland, 8 June 2004 (inaugural telemedicine lecture)
2. *Brain arteriovenous malformations*, Newcastle General Hospital, Newcastle, 20 May 2004
3. *Arteriovenous malformations of the brain*, Manchester Neuroscience Centre, Hope Hospital, Salford, 7 June 2002
4. *Confidentiality – practical tips on protecting patients, research & yourself*, 24th Advanced Clinical Neurology Course, Royal College of Surgeons, Edinburgh, 26 March 2002
5. *Vascular malformations of the brain*, Brain aneurysm self-help (BASH) patients' support group, Edinburgh, 25 February 2002
6. *Arteriovenous malformations of the brain*, Hurstwood Park Neurological Centre, Haywards Heath, 14 February 2002
7. *The natural history of brain arteriovenous malformations*, Bath Advanced Neurology course, 16 November 2001
8. *Arteriovenous malformations of the brain*, Walton centre for neurology and neurosurgery, Liverpool, 25 October 2000
9. *Submitting a multicentre ethics application: a researcher's perspective*, Scottish users' ethics review conference, 19 September 2000

Patient information leaflet

1. Al-Shahi R, Warlow CP. Vascular malformations of the brain. *Brain and Spine Foundation*

Abbreviations

95%CI	95% confidence interval
AOVM	Angiographically occult vascular malformation
AVM	Arteriovenous malformation
CHI	Community health index
CT	Computed tomography
DCN	Department of Clinical Neurosciences
FND	Focal neurological deficit
GP	General practitioner
GRO	General Register Office for Scotland
HHT	Hereditary haemorrhagic telangiectasia
IADSA	Intra-arterial digital subtraction angiography
ICD	International Classification of Diseases
ICeH	Intracerebral haemorrhage
ICrH	Intracranial haemorrhage
ISD	Information and Statistics Division
IVM	Intracranial vascular malformation
LREC	Local research ethics committee
MREC	Multicentre research ethics committee
MRI	Magnetic resonance imaging
SAH	Subarachnoid haemorrhage
SIVMS	Scottish Intracranial Vascular Malformation Study

Abstract

Arteriovenous malformations (AVMs) of the brain are part of the spectrum of intracranial vascular malformations (IVMs). They are the leading cause of intracerebral haemorrhage in young adults, they account for ~10% of non-traumatic subarachnoid haemorrhage, and they also cause epilepsy. Not only are affected individuals subject to the initial consequences of these events, but there are substantial risks of recurrent haemorrhage and epilepsy, and long-term disability.

For a disorder discovered as long ago as the mid-nineteenth century, surprisingly little is known about it. In this thesis, I begin by systematically reviewing the sizeable medical literature about brain AVM frequency, presentation, clinical course and prognosis. I did not find a single prospective, truly population-based study, which is why I set up the Scottish Intracranial Vascular Malformation Study (SIVMS) with the multidisciplinary collaboration of the four clinical neuroscience centres in Scotland.

SIVMS aspires to meet the standards of the ideal study of frequency and prognosis, by using multiple, overlapping sources of case ascertainment to prospectively recruit a population based inception cohort of adults, with explicit diagnostic criteria and outcome definitions for events which are validated by independent review. During 1999-2000, 96 adults (of whom 92 were definite) were detected with a first-in-a-lifetime diagnosis of a brain AVM in Scotland. Quality of baseline demographic, clinical and basic morphological data was excellent, although detailed variables about angioarchitecture were less complete, partly because only three-quarters of patients underwent catheter angiography. The cohort was distributed in proportion to the dispersion of the Scottish population, and standardised incidence ratios were not significantly different between healthboards. The sensitivity of ICD-10 coding of brain AVMs in hospital discharge data was 72% (95%CI 61% to 80%), and its positive predictive value was 46% (95%CI 38% to 55%). Reliance on hospital discharge data for case ascertainment or a requirement for catheter angiography to make the diagnosis would have biased the cohort. Furthermore, I found that expert neuroradiologists' assessment of AVM angioarchitecture on catheter angiography was characterised by greater intra-observer than inter-observer agreement (which ranged from less than chance for e.g. 'angiogenesis' to almost perfect for e.g. nidus size).

In a survey with multiple, overlapping sources of ascertainment confined to the Lothian healthboard region of Scotland, using capture-recapture analysis, I found the point prevalence of brain AVMs to be 18 (95%CI 16 to 24) per 100,000 adults. In SIVMS, the crude incidence of brain AVMs in Scotland in 1999 and 2000 was 1.1 (95%CI 0.9 to 1.4) per 100,000 adults per year. Of the incident adults, 53% were male and their median age at presentation was 45 years (range 16 to 81); one fifth were incidental discoveries and four fifths were symptomatic (presentation was with intracranial haemorrhage in 59%, one or more seizure(s) in 34%, and focal neurological deficits in 7%). 9% of cases were pure arteriovenous fistulae, 75% were lobar in location, 53% were superficial, and 22% had associated aneurysms. There appeared to be significant differences between SIVMS and well-established hospital-based cohorts.

Having established brain AVM prevalence, incidence and the characteristics of presenting adults, the next stage for this work is to describe prognosis for this enlarging population-based cohort. The data are being collected, the hurdles of ethical approval have been negotiated, although the direction in which privacy legislation and confidentiality guidance are heading will make this a challenging task.

Section 1: Background to the thesis

Chapter 1 Introduction

Chapter 2 Systematic review of studies of the frequency, clinical presentation and prognosis of brain arteriovenous malformations

Chapter 1. Introduction

Chapter contents

- 1.1 Early descriptions of brain arteriovenous malformations
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 - 1.3.4.1 Frequency
 - 1.3.4.2 Prognosis
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 - 1.3.6 Aetiology
- 1.4 Aims of this thesis

1.1 Early descriptions of brain arteriovenous malformations

The first description of arteriovenous malformations (AVMs) may be attributable to the ancient Egyptians, in the lengthy Papyrus Ebers, dating to the ninth year of the reign of Amenhotep I (~1534 BC) [Krayenbühl and Yasargil 1958], although a scholarly Egyptologist disputes this (John F Nunn, personal communication). Antyllus probably made the first mention of AVMs by distinguishing what he thought were two forms of aneurysm, one of which had an audible bruit [Osler 1915]:

There are two different kinds of aneurysms. The one kind occurs when there is a local dilatation of an artery (this was the origin of the name aneurysm or dilatation). The other kind arises from the rupture of an artery and the discharge of the blood into the flesh beneath it. Aneurysms due to the dilatation of an artery are longer than others; those due to a rupture are rounder. In the former there is a thicker layer of tissue; in the latter you can hear a certain crepitation if you press them with your finger; while in aneurysms due to dilatation there is no sound.

Following the death in the West of the science of the Greeks – a period when illness was thought to be due to an imbalance in the four humours of the body, and scholars pursued knowledge of god, not man – AVMs escaped medical attention for almost two millennia. The first case report of an extracranial AVM in a medical journal was made by William Hunter in the mid-eighteenth century [Hunter 1757], with subsequent elaboration [Hunter 1761].

Does it ever happen in surgery, when an artery is opened through a vein, that a communication, or *anastomosis*, is afterwards kept up between these two vessels? It is easy to conceive this case; and it is not long since I was consulted about one, which had all the symptoms that might be expected, supposing such a thing to have actually happened, and such symptoms as otherwise must be allowed to be very unaccountable. It arose from bleeding; and was of some years standing, when I saw it about two years ago; and I understand very little alteration has happened to it since that time. The veins at the bending of the arm, and especially the basilic, which was the vein that had been opened, were there prodigiously enlarged, and came gradually to their natural size, at about two inches above, and as much below the elbow. When emptied by pressure, they filled again almost instantaneously; and this happened even when a ligature was applied tight around the fore-arm, immediately below the affected part. Both when the ligature was made tight, and when it was removed, they shrunk, and remained of a small size, while the finger was kept tight

upon the artery, at the part where the vein had been open in bleeding. There was a general swelling in the place, and in the direction of the artery, which seemed larger, and beat stronger, than what is natural; and there was a tremulous jarring motion in the vein, which was strongest at the part that had been punctured, and became insensible at some distance both upwards and downwards.

[Hunter 1757]

It was not until the mid-nineteenth century that Luschka [Luschka 1854], and later others [Virchow 1863; D'Arcy Power 1888; Steinheil 1895], described *intracranial* AVMs. Rendu's first description of the syndrome now recognised as hereditary haemorrhagic telangiectasia (HHT) followed not long afterwards [Rendu 1896].

The spirit of medical enquiry in the nineteenth century, an era rich in diarists and scholars, often led to a close examination of not only their works, but also their brains (after their demise), to gain insight into both their brilliance and their illnesses. Thus we know that Gustave Flaubert [Gastaut and Gastaut 1982] and Paul Broca [Huard *et al.* 1982] may have had a brain AVM, Thomas Stamford Raffles had a dural AVM [Khoo *et al.* 1998], and Robert Louis Stevenson may have died due to a haemorrhage from a brain AVM secondary to HHT [Guttmacher and Callahan 2000] (Figure 1, page 49).

1.2 **The classification of brain arteriovenous malformations within the spectrum of intracranial vascular malformations**

1.2.1 *Early classification schemes*

Virchow made the first attempt to classify what are now referred to as intracranial vascular malformations (IVMs); he distinguished IVMs – which he assumed to be congenital – from tumours [Virchow 1863]. The nomenclature of the whole spectrum of IVMs first entered the medical lexicon when Virchow divided them into 'angioma cavernosum' and 'angioma racemosum' (the latter was subdivided into capillary, venous, arterial and arteriovenous types).

Following Virchow's classification, an array of synonyms was used to describe the category of arteriovenous shunting malformations, reflecting developments over time in

understanding their nature (see Appendix A of [Jellinger 1986]). Taxonomy has combined terms referring to their location (brain, cerebral, pial), vessel type (vascular, cerebrovascular, cerebral vascular, cirroid, arteriovenous, arterial venous, arteriovenous, angiomas), and the abnormality itself (neoplasm, angioma, aneurysm, anomaly, and malformation).

1.2.2 *Contemporary classification*

Advances in diagnostic radiology in the second half of the twentieth century have helped understand the anatomy and haemodynamics of IVMs, and have led to their increasing detection – and so an appreciation of their importance as a cause of death and long-term morbidity, mostly due to ICrH and epilepsy. The advent of cerebral catheter angiography [Moniz 1927], and brain imaging has popularised a morphological approach to the classification of IVMs. This has been reinforced by the apparent differences in prognosis and response to treatment between morphological subtypes.

The contemporary integrated classification shown in Table 1 (page 48) best reflects the main morphological groupings of IVMs, and fundamentally distinguishes ‘malformations’ (which have normal endothelial cell turnover and, if they grow at all, do so by hypertrophy) from ‘haemangiomas’, which grow by endothelial hyperplasia [Mulliken and Glowacki 1982].

1.3 **Brain arteriovenous malformations**

1.3.1 *Morphology*

A brain AVM is an anastomosis of mature arteries and veins – completely lacking intervening capillaries – within the brain parenchyma (Figure 2, page 50 and Figure 3, page 51). Arteriovenous shunting occurs through fistulae in a nidus (from the Latin *nidus*, meaning nest), which is the area towards which usually multiple feeding arteries converge, and from which one or more tortuous, dilated veins drain [Doppman 1971].

A brain arteriovenous fistula (AVF) is a type of brain AVM, but is distinguished by being a direct fistula between a single artery and one or more veins.

Aneurysms may exist on vessels within or feeding the nidus. Aneurysms are associated with brain AVMs in approximately 10% of patients in many series [Crawford *et al.* 1986a; Brown, Jr. *et al.* 1990; Westphal and Grzyska 2000; Al-Shahi *et al.* 2002a], although they are identified in up to 50% of patients in series with greater use of super-selective angiography and an endovascular treatment interest [Meisel *et al.* 2000].

1.3.2 *Nomenclature*

Some unity of terminology is required to overcome the historical variation in taxonomy, so I have chosen to use 'brain arteriovenous malformation.' The abnormality is a 'malformation' (it is not neoplastic, and therefore not an 'angioma'). The constituent vessels may be anywhere on the morphological spectrum between arteries and veins (the safest generalisation being 'arteriovenous'). Brain AVMs' location almost anywhere within the brain parenchyma makes 'pial' (with its connotations of the superficial cortical grey matter) and 'cerebral' (implying the telencephalon of the forebrain, and not more caudal structures) inappropriate terms.

This classification based on morphology, and location of the nidus or fistula, is less arbitrary than one based on the sources of afferent and efferent vessels, which are endlessly diverse [Morcos and Spetzler 1995]. Angiographic and pathological studies of the vascular anatomy ('angioarchitecture') and haemodynamics of AVMs have reinforced these simple morphological descriptions, but also illustrated the complexity of their anatomy [Houdart *et al.* 1993]. This has tempted some 'splitters' to reflect the complexity in brain AVMs' nomenclature, with subdivision using other terms referring to their radiological features (e.g. microangioma, micromalformation, cryptic vascular malformation, angiographically occult vascular malformation). By simply calling all of them, "brain AVMs", I have chosen to be a 'lumper' until such a time as these subgroups are found to reflect more than mere morphological variation.

The accurate distinction of brain AVMs from the other IVMs usually depends on careful and appropriate investigation using non-invasive and/or catheter imaging techniques.

1.3.3 Radiological features

1.3.3.1 Differentiating a brain AVM from normal brain and other pathologies

The widespread availability and immediacy of computed tomography (CT) pragmatically make it the first test an individual with a brain AVM might have at their initial presentation. Unenhanced CT may only show an asymmetry in tissue density to suggest a brain AVM (Figure 4A, page 52), and smaller brain AVMs can be missed altogether. Enhanced CT is probably a more sensitive investigation, because it may reveal the dilated vasculature of an AVM (Figure 4B, page 52) with a serpiginous pattern of contrast enhancement [Kumar *et al.* 1984]. On the other hand, the specificity of CT, either with or without enhancement, is affected by the occasional difficulty in distinguishing an AVM from a low-grade glioma, especially when the AVM is thrombosed [Wharen, Jr. *et al.* 1982]. The particular strengths of magnetic resonance imaging (MRI) lie in its evaluation of AVM nidus size [Noorbehesht *et al.* 1987] and its anatomical relationships (Figure 4C&D, page 52). Modern intra-arterial digital subtraction angiography (IADSA) is regarded by most as the diagnostic reference standard [Joint Writing Group 2001], and demonstrates rapid contrast opacification of the nidus in the early capillary/venous phase (Figure 5, page 53). The specificity of both MRI and IADSA is affected by the occasional similarity of neoplasms to AVMs. Occasionally CT or MRI appearances suggest an IVM that is not demonstrated on complete IADSA at all. These 'cryptic' or 'angiographically occult' vascular malformations (AOVMs), when subjected to pathological examination, are morphologically heterogeneous, but cavernous malformations (CMs) and small brain AVMs are the main contributors [Lobato *et al.* 1988; Robinson, Jr. *et al.* 1993; Tomlinson *et al.* 1994; Hallam and Russell 1998].

There is, therefore, no single definitive investigation for brain AVMs, which means that existing evaluations of the diagnostic accuracy of any imaging modalities do not have a reference standard, but rely on pathological confirmation or direct comparisons of different techniques [Pott *et al.* 1992]. Despite the recognition of these sources of error, there are no adequate studies (because they have been small, retrospective and

radiologists were usually not blinded to clinical features) evaluating the sensitivity and specificity of MRI or IADSA against any reference standard for the detection of brain AVMs.

1.3.3.2 Detecting a brain AVM underlying intracranial haemorrhage

The investigation of intracerebral haemorrhage (ICeH) with unenhanced CT has a sensitivity for identifying an underlying brain AVM of between 50% and 77% and a specificity between 84% and 99%, when compared against a reference standard of IADSA, with or without pathological confirmation [Halpin *et al.* 1994; Hayward and O'Reilly 1976; Laissy *et al.* 1991]. However, some of these studies have been limited by being retrospective and unblinded, with selected patient groups, varying CT matrix sizes, and inconsistent use of intravenous contrast.

Although there are, as yet, no adequate studies of MRI as a diagnostic test in identifying an underlying cause for an ICeH, it is a helpful investigation in its follow-up [Meyer and Gorey 1998], especially in the context of recurrent ICeH [Heier *et al.* 1986].

The usefulness of IADSA in the investigation of ICeH has been studied in terms of its diagnostic yield. Some of these studies have been retrospective and reported on the same series of patients [Toffol *et al.* 1986; Loes *et al.* 1987]. But even when prospective, other studies have been conducted on highly selected groups of patients [Zhu *et al.* 1997], so unsurprisingly the authors of these studies have drawn varying conclusions. On the basis of the available evidence, for the further investigation of a suspected brain AVM (or other underlying condition) as a cause of ICeH demonstrated on CT, a minimum standard is IADSA in everyone apart from those over 45 years of age with both pre-existing hypertension and haemorrhage in deep locations [Zhu *et al.* 1997]. Early IADSA may not reveal some brain AVMs underlying ICeH, presumably because of their compression by haematoma, so a normal IADSA close to the onset of an ICeH should be supplemented by delayed IADSA or MRI, although which should be used, and when, is debatable [Lemme-Plaghos *et al.* 1986; Halpin *et al.* 1994; Sigal *et al.* 1990; Willinsky *et al.* 1993]. Of course, these algorithms may be superseded by the need for surgical intervention, and their appropriateness may depend on the clinical condition and age of the patient. The investigation of subarachnoid haemorrhage (SAH) with CT

and adequate IADSA is widely accepted, but the value of repeat IADSA is questionable, and MRI might be helpful if an underlying brain AVM is strongly suspected, although this strategy has not been formally evaluated. A second IADSA tends to be recommended only if the patient suffers a recurrent haemorrhage, or if the initial examination was technically inadequate, affected by vasospasm or did not cover both carotid and both vertebral arteries [du Mesnil de Rochemont *et al.* 1997; Forster *et al.* 1978; Gilbert *et al.* 1990; von Holst *et al.* 1988].

1.3.3.3 Brain AVM angioarchitecture

There is a growing literature on angioarchitecture [Valavanis 1996; Houdart *et al.* 1993], haemodynamics [Kader and Young 1996], and an interest in creating artificial models of brain AVMs to better understand their haemodynamic complexity [Gao *et al.* 1998], including unusual outcomes such as spontaneous regression without treatment [Nehls and Pittman 1982]. Whilst IADSA may only be necessary to establish diagnostic certainty in some cases, the interest in how angioarchitecture and haemodynamics might determine prognosis has made it a requisite, and often an entry criterion, for some studies of the clinical course of brain AVMs.

The principal angioarchitectural features of interest are illustrated in a schematic diagram in Figure 6, page 54. However, objective definitions of the variations in angioarchitecture have been unclear and inconsistent until recently [Joint Writing Group 2001], and experts disagree about their existence and prognostic value. Furthermore, the accuracy of detailed angioarchitectural information may depend not only on inter- and intra-observer variation, but also on the use of super-selective IADSA, which involves the coaxial catheterisation of individual arterial branches with flow-guided or wire-guided microcatheters. By avoiding the superimposition of other arterial vessels, this technique may better determine the type of feeding artery and the detailed angioarchitecture of the nidus. In some radiologists' hands, super-selective IADSA is used for measurement of arterial pressures if coupled to a pressure transducer, and also for functional localisation by the injection of barbiturate [Viñuela *et al.* 1984].

1.3.4 *Burden*

1.3.4.1 Frequency

Prior to systematically reviewing the literature (Chapter 2), I was aware of only one truly population-based (albeit retrospective) study of the incidence of brain AVMs. This study was based on the population of Olmsted County, Minnesota, USA (~124,000) over 27 years, used the comprehensive Mayo Clinic Medical Records Linkage system, and found a brain AVM incidence of ~1 per 100,000 person-years [Brown, Jr. *et al.* 1996b]. I knew of no reliable estimates of brain AVM prevalence.

At least half the adults newly diagnosed with a brain AVM present with ICrH, thereby accounting for approximately one third of all non-traumatic ICrH in young adults [Ruíz-Sandoval *et al.* 1999].

1.3.4.2 Prognosis

Based on the population-based data available so far, the risk of death is greatest in the month following a first-ever haemorrhage from a brain AVM, with a 30-day case fatality of ~18% [Brown, Jr. *et al.* 1996a]. This relatively low early case fatality and a subsequent annual case fatality of ~1% is likely to leave a sizeable prevalent burden of adults with long-term disability, potentially exposed to the risks of recurrent haemorrhage and/or epilepsy, due to the disease itself or its treatment.

1.3.5 *Treatment*

Until the end of the nineteenth century brain AVMs were not treated because there were no known therapies. ‘Conservative management’ continues to be appropriate for some people with brain AVMs, although the development of neurosurgical, endovascular and radiation treatment has led to their use alone or in combination for selected individuals.

Neurosurgical exposure of brain AVMs was first reported around the turn of the twentieth century [Giordano 1890; Krause 1908]. In 1928 Cushing and Bailey wrote, “to

extirpate one of these aneurysmal angiomas in its active state would be unthinkable...” [Cushing and Bailey 1928], but whilst their book was in press Walter Dandy published a case series of 8 patients of his own treated surgically, and 22 similar cases from the literature [Dandy 1928]. Subsequent developments in catheter angiography, bipolar coagulation, the operating microscope and stereotactic surgery have encouraged surgical intervention and probably improved the completeness and safety of resection [French 1977].

Endovascular embolisation of brain AVMs, by injecting artificial agents in the afferent blood supply, was first reported in 1960 [Luessenhop and Spence 1960]. The technique has been refined ever since [Luessenhop *et al.* 1965], initially as an adjunct to neurosurgical excision [Wolpert and Stein 1975], but more recently – with the development of liquid polymer glues – as a potentially curative procedure.

Stereotactic radiotherapy came into use a decade later [Steiner *et al.* 1972], initially advocated for small brain AVMs, and later in conjunction with other therapies for larger brain AVMs, using both the Leksell gamma knife and linear accelerator techniques.

The pace of development of endovascular, surgical and radiation therapies during the late twentieth century, combined with considerable conviction amongst interventionists about their clinical- and cost-effectiveness in the absence of randomised controlled trials, must have led to an increasing burden on health service budgets [Sellar 2000; Al-Shahi and Warlow 2003].

1.3.6 *Aetiology*

The aetiology of a condition is conventionally discussed ahead of morphology, classification and treatment, but in the case of brain AVMs I leave it until last because even less is known about their cause.

Most theories about the cause(s) of brain AVMs have been postulations about persistence or redevelopment of an embryonic arteriovenous connection [Mullan *et al.* 1996; Truwit 1994; Jellinger 1986]. A congenital origin is thought to be supported by the absence of features of neoplasia and the co-existence of brain AVMs with aneurysms, as well as with other types of IVM, congenital anomaly and dysplasia [Warkany and Lemire

1984; Jellinger 1986]. The evidence that brain AVMs detected in adults are always present from birth was thought to be incomplete [Lasjaunias 1997], but there are reports of their prenatal detection using foetal ultrasound [Auyeung *et al.* 2003]. It is likely that brain AVMs are usually too small to be detected by this means, unless they are associated with grossly distorted angioarchitecture such as venous varices, or colour Doppler is used [Dan *et al.* 1992]. The diversity of brain AVMs' biological behaviour (such as *de novo* appearance, spontaneous regression and evolution with time) has led to scepticism about their assumed congenital origin, although their postnatal growth could simply be stimulated by some trigger (e.g. haemodynamic, vascular remodelling, hormonal, or traumatic etc.) [Nussbaum *et al.* 1998; Lasjaunias 1997].

Whether the development of a brain AVM occurs *in utero* or not, an underlying genetic mechanism – at least in some cases – is suggested by their occurrence in two or more members of some families and in families with the autosomal dominant condition HHT [McAllister *et al.* 1994; Herzig *et al.* 2000]. There are no twin studies of apparently sporadic brain AVMs. How much any putative genetic mechanism accounts for sporadic brain AVMs is speculative.

1.4 Aims of this thesis

Now that brain AVMs can be distinguished clearly from other IVMs on morphological grounds, using imaging techniques that are in increasingly widespread use, at a time when too little is known about their prognosis yet there is rapid development in expensive and sometimes risky interventions, there seems a pressing need to re-examine the epidemiology of brain AVMs. Their burden of disability, death, economic hardship and loss of quality of life is likely to be considerable (1.3.4, page 44), and I will show that the quality of existing research is poor (Chapter 2).

Information about the proportions of any population newly diagnosed with a brain AVM over a period of time (incidence), or living with the diagnosis at a single point in time (prevalence), are sparse. These measures would help to provide fundamental information on disease burden for healthcare planning and comparison with other populations. The clinical course of brain AVMs in general and, more so, the prognosis for individuals are uncertain, as are the risks and benefits of the available treatments,

perpetuating inevitable variation in treatment practice and disagreement about the need for randomised trials.

To help address these uncertainties, in 1998 I set up a prospective, inception cohort study of adults newly diagnosed with any type(s) of IVM in the Scottish population – the Scottish Intracranial Vascular Malformation Study (SIVMS). Intriguingly, during the time span of my thesis, research interest in the population-based frequency and clinical course of brain AVMs appeared to grow [Berman *et al.* 2000]. I visited the Columbia AVM research group at the Neurological Institute of New York, USA to find that they were in the process of setting up a similar incidence study, due to start a year after SIVMS, in the New York Islands (<http://cpmcnet.columbia.edu/dept/avm>).

This thesis is based on every adult with a brain AVM during the first two years (1999-2000) of SIVMS, and aims to address the following questions:

- What is the quality of existing studies of brain AVM frequency and prognosis, and what are their findings (Chapter 2)?
- What is the design of SIVMS, and what clinical and morphological variables does it collect (Chapter 3 to Chapter 6)?
- How complete is case ascertainment in SIVMS, is it truly population-based, and what is the quality of its data (Chapter 7 to Chapter 9)?
- How well do experienced observers agree in their interpretation of morphological variables of brain AVMs observed on IADSA (Chapter 10)?
- What is the prevalence of brain AVMs among adults in Scotland (Chapter 11)?
- What is the incidence of brain AVMs in adults in Scotland (Chapter 12)?
- How do incident brain AVMs present, and what are their morphological characteristics when first diagnosed (Chapter 13 and Chapter 14)?
- What are the future directions for SIVMS (Chapter 15)?

Table 1 An integrated classification scheme for vascular malformations of the brain

From [Chaloupka and Huddle 1998]

Benign proliferating vascular anomaliesHaemangioma

Non-proliferating vascular anomalies

Capillary malformation (telangiectasis)

Venous malformation (developmental venous anomaly)

Cavernous malformation (cavernoma)

Arterial malformation (angiodysplasia and aneurysm)

Arteriovenous shunting malformations

Brain arteriovenous malformation

Brain arteriovenous fistula

Dural arteriovenous malformation

Vein of Galen arteriovenous fistula

Mixed malformations

Figure 1 Notable sufferers from brain arteriovenous malformations

A: Paul Broca (1824-1880), French neurologist renowned for his localisation of the motor speech area to the inferior frontal gyrus, died from a brain haemorrhage, thought to be due to rupture of a brain AVM [Huard *et al.* 1982]

B: Gustave Flaubert (1821-1880), French novelist of the realist school famous for *Madame Bovary*, suffered intractable epilepsy and died from a brain haemorrhage, both thought to be due to a brain AVM [Gastaut and Gastaut 1982]

C: Robert Louis Stevenson (1850-1894), Bohemian Scottish author famed for works such as *Treasure Island*, may have died due to a haemorrhage from a brain AVM secondary to hereditary haemorrhagic telangiectasia (HHT) [Guttmacher and Callahan 2000]

D: Sir Thomas Stamford Raffles (1781-1826), founder of Singapore, had a right frontal dural AVM that caused hyperostosis of the skull – which he tried to mask with his distinctive hairstyle – and which led to his death from a brain haemorrhage [Khoo *et al.* 1998]



Figure 2 Schematic diagram of a brain AVM, with an aneurysm on a feeding artery, in the right frontal lobe (sagittal view)

F = two arterial feeding vessels; A = feeding artery aneurysm; N = nidus;
V = three draining veins

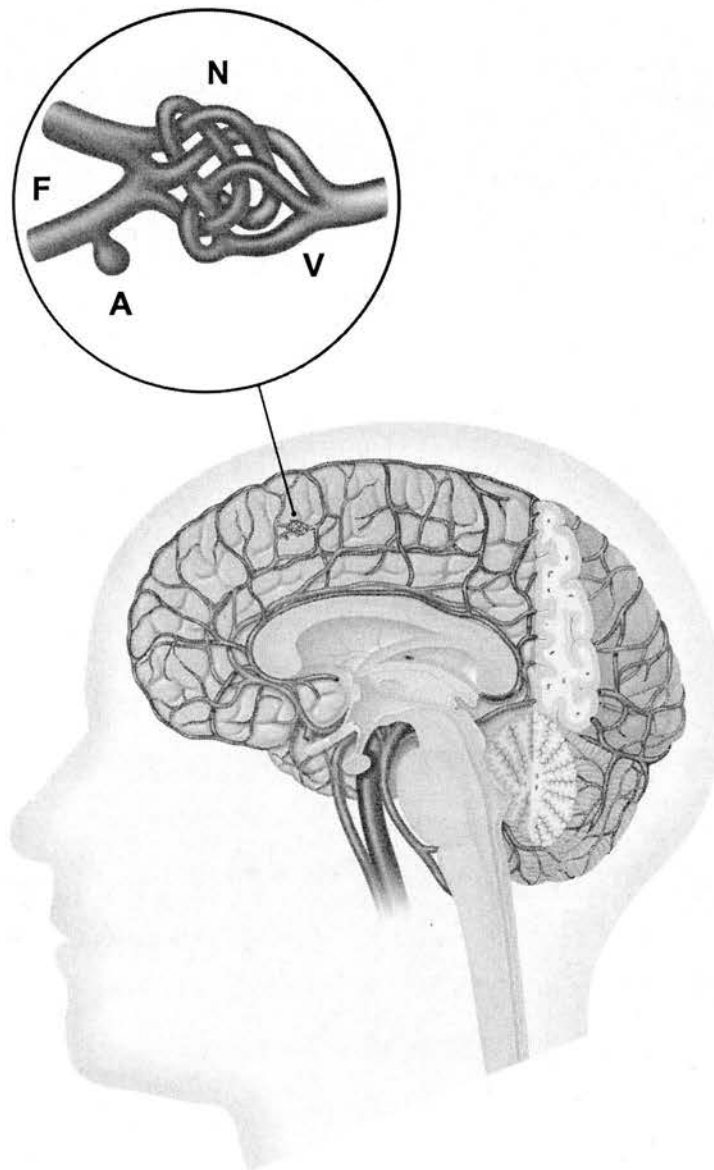


Figure 3 Illustrations of brain AVM macroscopic pathology

A: Autopsy specimen of a brain AVM lying superficially in the cortex of the right temporal lobe

B: Surgically resected brain AVM illustrating vessels of varying calibre

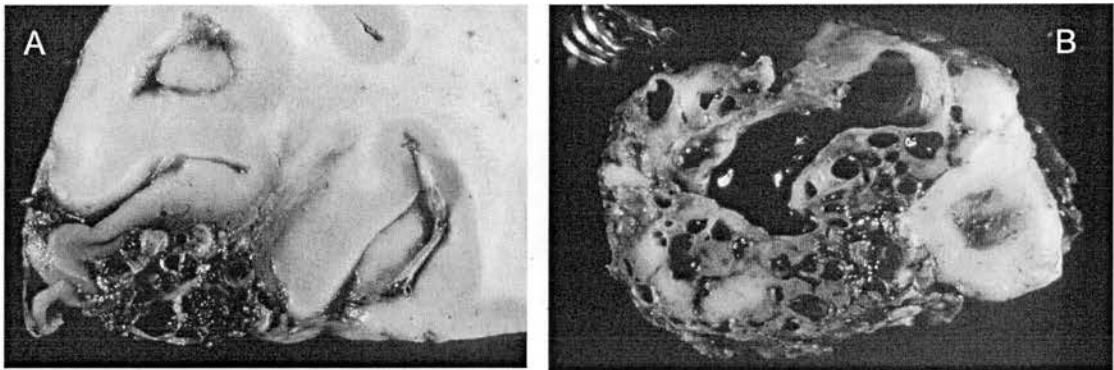


Figure 4 Computed tomography (CT) and magnetic resonance imaging (MRI) of brain AVMs

CT of the brain in the axial plane without (A) and with (B) intravenous contrast demonstrates a brain AVM in the right temporal lobe. Coronal, unenhanced, T1-weighted MRI demonstrates a brain AVM in the left parietal lobe (C). Axial proton density MRI demonstrates a brain AVM in the midbrain and right thalamus (D)

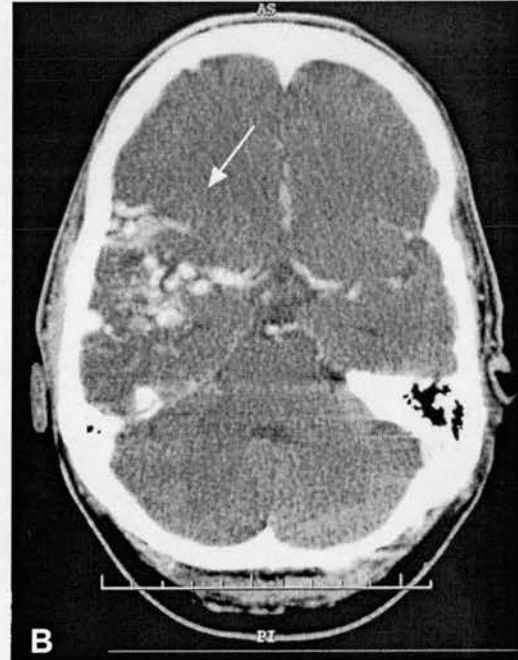
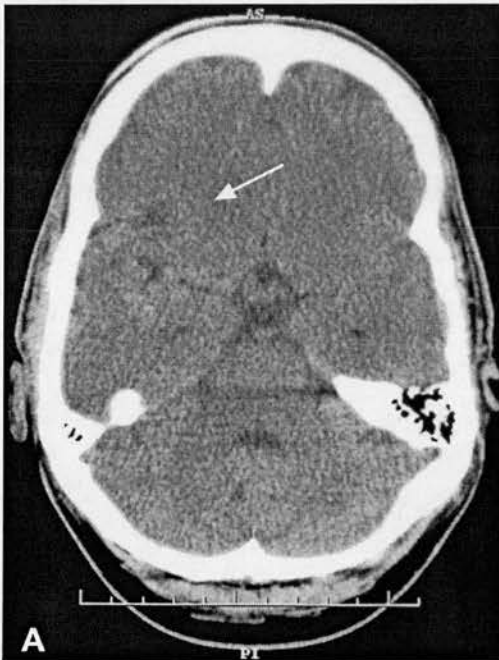


Figure 5 Lateral projections of intra-arterial digital subtraction angiograms (IADSA) of the normal cerebral vasculature (left) and a brain AVM (right, arrowed)

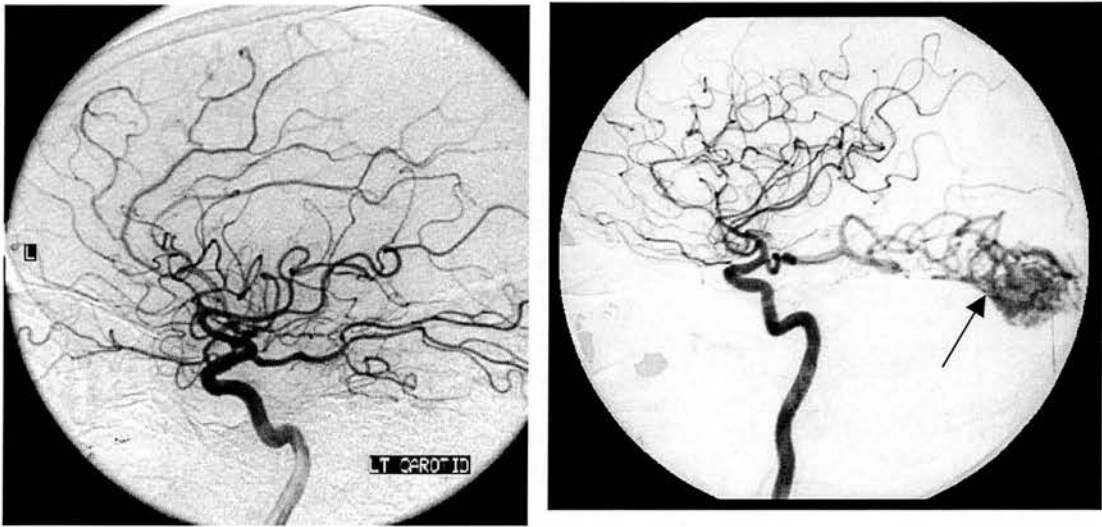
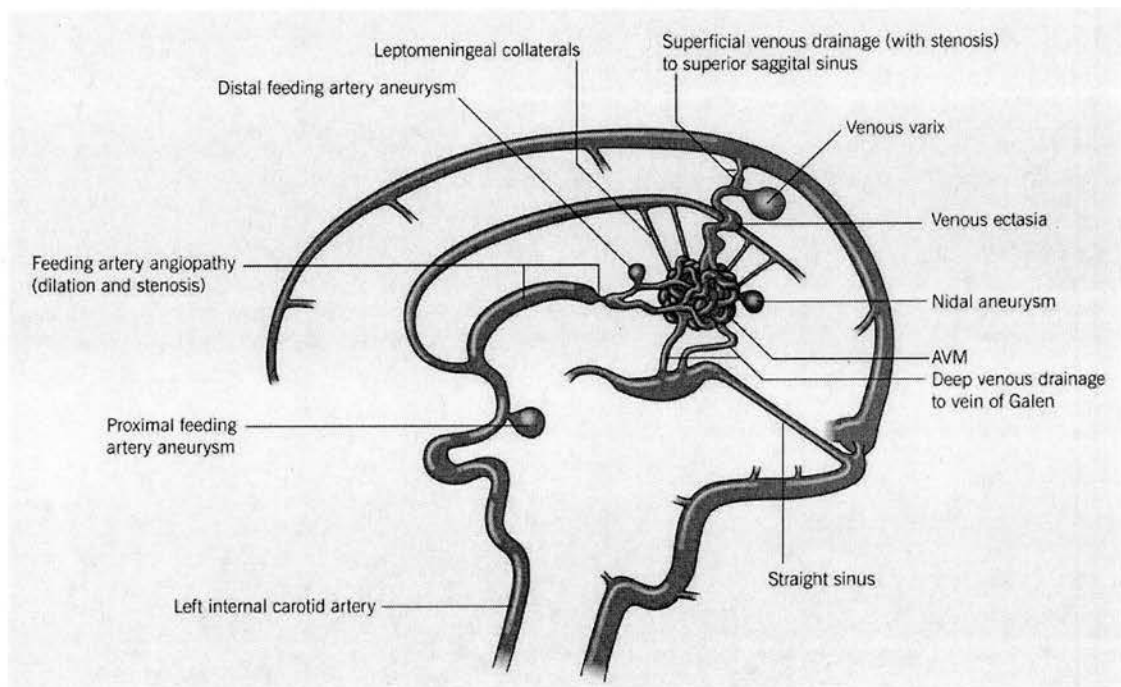


Figure 6 Schematic diagram of brain AVM angioarchitecture

Chapter 2. Systematic review of studies of the frequency, clinical presentation and prognosis of brain arteriovenous malformations

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2.1 Introduction

Although there have been *narrative* reviews of the frequency and clinical course of brain AVMs [The Arteriovenous Malformation Study Group 1999; Stapf and Mohr 2000], there have been no *systematic* reviews. I have redressed this deficit by gathering all the available research on brain AVMs in adults using thorough search methods, critically evaluating the literature against objective methodological criteria, and summarising the best studies according to modern standards in observational epidemiology [Stroup *et al.* 2000; Al-Shahi and Warlow 2001]. I have tried to straddle the objective statistical technique of meta-analysis and the subjective art of a traditional narrative review, largely because the heterogeneity of the included studies in their design and reporting has precluded a quantitative synthesis [Slavin 1995; Centre for Reviews and Dissemination 1996].

2.2 Methods

Using strict criteria to judge the quality of methods and reporting, I have selected the highest quality studies from an exhaustive systematic electronic and hand search of the medical literature.

2.2.1 Literature search

I sought any publication about brain AVMs in Medline (*Index Medicus* online, American Library of Medicine, from 1966) and Embase (*Excerpta Medica* online, Bath Information Data Services, from 1980) to the end of February 2001, and in the Cochrane Library 2001, Issue 1, using a 14-line search strategy (Table 2, page 83). This strategy had 94% sensitivity when evaluated against a hand search of the two journals in which the largest number of studies of brain AVMs have been published (*Journal of Neurosurgery* and the *American Journal of Neuroradiology*) (Table 3, page 84) [Dickersin *et al.* 1994].

I also searched other databases, registries of clinical trials and research in progress (the MRC Clinical Trials Directory, the National Research Register (NRR) and Cochrane Controlled Trials Register). Publications antedating 1966, and others missed by the

search, were sought by scanning the bibliographies of retrieved articles, and by surveillance of paper and electronic journals.

Nearly ten thousand publications were found by this combination of search methods (Figure 7, page 91). By scanning their abstracts, I found approximately 3000 to be germane to the scope of the systematic review. Because of the difficulty in reliably limiting a literature search about a condition using a search strategy for studies of its prognosis [Altman 2001b], the titles and available abstracts of all 3000 papers were scrutinised using a bibliographic software package (Reference Manager® Version 9.0N, Research Information Systems), and those of apparent relevance were read in full [Pitkin *et al.* 1999].

I did not seek unpublished data (it is uncertain whether bias is reduced or increased by including such data), nor did I try to obtain individual patient data. I was alert to publication bias in its many forms: English language bias, database bias, citation bias, multiple publications from single studies, republication of existing series following accrual of additional cases, and speciality bias [Easterbrook *et al.* 1991]. These sources of bias are likely to be masked by the other biases of a predominantly observational literature.

2.2.2 *Critical appraisal*

I used methodological quality filters based on explicit criteria, with corresponding data collection forms, to guide my assessment of studies' validity [Sackett *et al.* 1991; Laupacis *et al.* 1994; Dixon *et al.* 1997]. I was aware that any assessment of a study's quality is a subjective process (largely because the reporting of methods is often inadequate for this purpose), so where there was doubt about a particular study, my supervisor independently appraised it [Egger and Smith 1998].

I have chosen to cite only those studies whose results are least likely to be affected by systematic bias, confounding, and chance in their design and conduct. The criteria for including studies in my analysis are specified below; because the studies did not remotely resemble an ideal study of prognosis, these criteria were used for guidance, and an absolute requirement for an included study to meet a certain number of criteria was impossible.

2.2.2.1 Incidence and prevalence studies

I sought large, unselected, prospective, population-based studies, whose internal and external validities were enhanced by a standard definition of what actually constitutes a brain AVM, and adequate brain imaging to detect it. If there were no population-based data meeting these criteria, I chose to resort to the best available hospital-based studies of brain AVM frequency, recognising that these are likely to be unrepresentative of the population (because of selection bias and under-ascertainment of particularly severe or particularly mild cases). If no prospective studies were available, I resorted to the existing retrospective data.

2.2.2.2 Studies of clinical presentation

A representative assessment of the way brain AVMs manifest themselves should also be undertaken in population-based samples. But, because of the paucity of population-based data on brain AVMs, I have had to include hospital-based studies without an explicit treatment selection bias. I have selected those with more than one hundred – preferably consecutive – patients and, for each and every individual, an explicit allocation to a *single* dominant mode of presentation at diagnosis. In view of the republication of some eligible studies following the accrual of additional people, and occasional duplicate publication, I have restricted my analysis to the largest single series from each hospital meeting these criteria.

2.2.2.3 Studies of prognosis

To explore the recognised heterogeneity of brain AVM prognosis and establish the behaviour of the ‘average patient’, the clinical course of large, representative samples of people with brain AVMs needs to be investigated. Insights into the factors that predict and explain future risk can be gleaned from such studies to help estimate the prognosis for any individual person. With this knowledge, stratification of individuals according to their subsequent risk of death (due to ICrH, for example), or their risk of the future occurrence of ICrH, epilepsy, focal neurological deficit (FND) and cognitive impairment, might help decide whether they should be considered for treatment or not.

However, the findings of studies of prognosis are extremely susceptible to imperfections in study design, which makes a careful appraisal of study methods essential.

The criteria that have guided my selection of the best available studies of the clinical course and prognosis of brain AVMs are based on published guides [Sackett *et al.* 1991; Laupacis *et al.* 1994]; given the paucity of these guides, I supplemented them with expert opinions of members of my department. These criteria subsume many of the aforementioned requirements of studies of brain AVM frequency and clinical presentation (Table 4, page 85).

Adequate radiological or pathological investigation should have been used to reliably diagnose a brain AVM according to a clear, explicit definition, so that the study sample was not contaminated by dural AVMs or other types of IVM. The sample should be followed prospectively from an early and uniform ('inception') point in the clinical course of the disease. The most meaningful and practical point to standardise as 'zero time' is the time of first-ever brain AVM diagnosis, bearing in mind that diagnosis may well be occurring earlier nowadays, perhaps making prognosis seem better than before because of lead-time bias. The alternative of choosing the first-ever symptom as the inception point would often involve retrospective data collection, whilst the other alternative of choosing the first presentation to a particular hospital is not uniform because it could occur at any time after the onset of someone's symptoms.

The individuals being studied should be a representative sample, preferably from a well-defined population including people diagnosed at smaller hospitals and those who died in the community. Studies at tertiary referral centres are likely to represent people who have survived their initial presentation with more aggressive disease, and this sort of sampling bias affects prognostic sub-groups unequally [Hofmeister *et al.* 2000].

Again, my choice of sample size has been set arbitrarily at a minimum of 100 people, to maximise the precision of the studies' results, and to increase the power to detect, at best, large effects. The number of outcome events is the main determinant of the power of a study of prognosis, but because outcome events for brain AVMs are relatively infrequent, and by being treated many people will be censored from an actuarial analysis before the occurrence of an outcome, a large sample size is all the more important. This size cut-off was also chosen because the methodological quality of studies of fewer than 100 people was so poor, with only 2 exceptions (Table 7 to Table 9).

The outcomes studied should be clinically important (such as death and morbidity from ICrH and epilepsy), and their objectivity should be enhanced by clear definitions or the use of generic outcome measures. The assessment of morbidity should preferably be blinded to the prognostic factors under investigation (to minimise the effect of measurement bias due to clinicians' prior expectations), and it should be as accurate and consistent as possible with, for example, radiological evidence of ICrH. Moreover, in view of the current tendency to treat brain AVMs once they are discovered, the assessment of outcome should be stratified according to any therapeutic intervention during follow-up. When outcome measures are used to evaluate impairment, disability, handicap or health-related quality of life, their validity, reliability and responsiveness for people with brain AVMs should have been demonstrated.

Follow-up should be prospective and as complete ($\geq 90\%$) as possible, starting at the inception point in all cases. Incomplete follow-up jeopardises study results, as the reasons for it are often linked to important prognostic outcomes. Follow-up needs to be lengthy, especially because the average interval between ICrH from brain AVMs may be ~ 8 years [Ondra *et al.* 1990; Hartmann *et al.* 1998]. Although an analysis of prognostic outcome as an annual rate, averaged over the period of the study, has the virtues of simplicity and ease of comparison across studies, it obscures variation between patient subgroups and over time. For example, the prognosis for a dichotomous variable such as dead versus alive can be evaluated at a specific time (e.g. at one year after diagnosis) or as a proportion of people affected (e.g. case fatality). On the other hand, using an actuarial analysis (e.g. time to death) and plotting a survival curve, provides far more enlightening information about the pattern over time, which would otherwise be lost in an annualised survival rate.

Studies of the average clinical course for people with brain AVMs can be used to identify factors that may help predict the prognosis of a particular event for a specific individual. Continuous predictor variables should be kept as such, avoiding arbitrary cut-offs [Altman 2001b]. The evaluation of prognostic factors should include not only their statistical significance, but also their clinical significance in terms of an odds ratio or relative risk, with 95% confidence intervals. Disentangling true *determinants* of prognosis from those merely *associated* with particular outcomes in a univariate analysis is difficult. Insights into clinically useful *predictors* of outcome, which may be either

associated with particular outcomes or actual determinants of them, can be gleaned from a multiple regression analysis, although stratification may be useful in simpler situations. For outcomes that are binary or time to a specific event, logistic or Cox proportional hazards regression models respectively are appropriate for examining the influence of several prognostic factors simultaneously [Altman 2001b]. These models are not accurate unless there are adequate numbers of subjects and outcome events per variable studied [Sackett *et al.* 1991; Peduzzi *et al.* 1996], nor are they generalisable unless their robustness has been externally validated in other brain AVM populations. Systematic reviews of such studies are particularly difficult because the outcome of interest is often the time to an event, the variable of interest is often one of many putative prognostic factors, and many of these are continuous variables for which there are a variety of methods of analysis [Altman 2001a; Altman 2001b].

2.3 Results

2.3.1 Frequency

I have summarised the best studies of the incidence and prevalence of brain AVMs in unselected populations. Data about brain AVM prevalence in selected disease groups were easier to find, so I applied the same selection criteria to samples of people with stroke, ICeH, SAH, epilepsy, headache and HHT (Figure 8, page 92).

2.3.1.1 Incidence in unselected populations

In the published literature, there is only one population-based study of brain AVM incidence, although it was retrospective [Brown, Jr. *et al.* 1996b], and there are other studies which purport to measure incidence, but are not truly population-based [Jessurun *et al.* 1993]. The earliest study was based in the only hospital serving a population of 155,000 living on the islands of Curaçao and Bonaire in the Dutch Antilles, between the years of 1980 and 1990 [Jessurun *et al.* 1993]. The crude incidence of people of any age affected by an AVM over the ten-year period was 1.1 (95%CI 0.6 to 1.8) per 100,000 person-years. However, this study is only approximate because there

was just one source of case ascertainment, sudden deaths in the community due to as yet undiagnosed AVMs were unaccounted for, information about the means of brain AVM identification was scanty, all cases were symptomatic, and there was an unusually high frequency of multiple AVMs (probably attributable to the large proportion of people with HHT). The later study used the comprehensive Mayo Clinic Medical Records Linkage system to identify 26 brain AVMs over a period of 27 years in Olmsted County, Minnesota [Brown, Jr. *et al.* 1996b]. The age- and sex-adjusted incident brain AVM detection rate was 1.1 (95%CI 0.7 to 1.5) per 100,000 person-years between 1965 and 1992. However, the brain AVM detection rate increased over time due to the escalating use of progressively more advanced brain imaging during the study period.

2.3.1.2 Prevalence

2.3.1.2.1 Unselected populations

Until now, there have been no studies of the prevalence of brain AVMs in unselected populations, although large post mortem series have been used to attempt to estimate the prevalence of both symptomatic and clinically silent brain AVMs. Hospital-based post mortem series have reported brain AVM prevalences up to 600 per 100,000 [Sarwar and McCormick 1978; Courville 1950; Jellinger 1986]. However, the method of cohort selection and the thoroughness of lesion ascertainment during pathological examination are potential and often insuperable biases.

2.3.1.2.2 Stroke

There have been several population-based studies of the frequency of stroke, but their primary aim was not to describe the frequency of brain AVMs as a cause of stroke. It was therefore unsurprising that, of eight comparable stroke incidence studies performed in the modern era of brain imaging meeting strict methodological criteria and providing data about pathological subtypes, none commented on brain AVMs as a cause of stroke [Sudlow and Warlow 1997]. For example, the Oxfordshire Community Stroke Project found that 10% of first-ever-in-a-lifetime strokes were due to primary ICeH, but no

underlying brain AVMs were found because the use of MRI was infrequent, and only two people with primary ICeH ever had IADSA [Bamford *et al.* 1988; Bamford *et al.* 1990; Boonyakarnkul *et al.* 1993].

I therefore sought prospective, hospital-based studies with adequate rates of CT (>90%) and the appropriate use of IADSA, at least, to give a rough estimate of the frequency of brain AVMs as a cause of first-ever-in-a-lifetime stroke. Even then, only two stroke registries provided any information about brain AVMs. The Lausanne Stroke Registry is a prospective study of people with first-ever-in-a-lifetime stroke, excluding SAH [Bogousslavsky *et al.* 1988]. By imaging every patient with CT, and almost a third of all strokes with IADSA, brain AVMs were detected in 1.4% (95%CI 0.8% to 2.3%). I excluded the Harvard Co-operative Stroke Registry from my analysis because CT was not widely used, and brain AVMs were lumped with aneurysms as a cause of stroke.

I applied similar selection criteria to eight studies giving information about brain AVMs as a cause of first-ever-in-a-lifetime stroke in young people, whose ages generally ranged from a minimum of 15 years to a maximum of 44 years. The only truly prospective, population-based study found that brain AVMs account for roughly 3% (95%CI 1% to 11%), of first-ever-in-a-lifetime strokes in young adults [Nencini *et al.* 1988; Radhakrishnan *et al.* 1986]. Several retrospective hospital-based series were excluded because they were not explicit about studying first-ever-in-a-lifetime strokes, did not specify the extent of brain imaging, or combined brain AVMs and aneurysms in one aetiological category.

2.3.1.2.3 Intracerebral haemorrhage

Overall, approximately 10% of first-ever-in-a-lifetime strokes in Whites are caused by primary ICeH [Bamford *et al.* 1990; Thrift *et al.* 1995]. The importance of primary ICeH, and of brain AVMs as a cause, has been recognised since the increasingly widespread use of CT in the early investigation of stroke [Broderick *et al.* 1989]. Many studies have varied in the extent of their further investigation of an underlying cause, and their inclusion criteria by aetiology or location of haemorrhage.

There is a paucity of satisfactory population-based data on the frequency of brain AVMs as a cause of first-ever-in-a-lifetime primary ICeH. The only truly population-based

study was retrospective, and was performed before the CT era, although it did use the comprehensive Mayo Clinic Medical Records Linkage system to study cases of first-ever primary ICeH in Rochester, Minnesota, of which 4% (95%CI 2% to 8%) were attributable to brain AVMs [Furlan *et al.* 1979]. Four other studies were hospital-based, of which two did not explicitly study first-ever-in-a-lifetime primary ICeH, and the two others combined brain AVMs with the other IVMs in one aetiological group. Two retrospective autopsy studies of fatal spontaneous primary ICeH found an underlying brain AVM in 15% to 16% of cases, probably an over-estimate due to case selection bias [McCormick and Rosenfield 1973; Jellinger 1977].

There are no population-based studies, either prospective or retrospective, of the frequency of brain AVMs as a cause of first-ever-in-a-lifetime primary ICeH in young people. The best available estimate comes from a retrospective, hospital-based study of people under 40 years of age with primary ICeH, that confirmed brain AVMs with MRI or IADSA in all cases [Ruíz-Sandoval *et al.* 1999]. In this study, brain AVMs were the leading cause of primary ICeH in the young, affecting 33% (95%CI 27 to 40%) of people. Four other similar, retrospective hospital-based studies did not specifically study first-ever-in-a-lifetime primary ICeH, and their IADSA rates ranged from 40% to 85%.

2.3.1.2.4 Subarachnoid haemorrhage

In Western populations, the most frequent cause of spontaneous SAH is rupture of a saccular aneurysm on or near the Circle of Willis. One recent prospective, population-based study in Norway, that studied every person with CT and 76% with IADSA, found brain AVMs caused 9% (95%CI 5% to 18%) of SAH [Kloster 1997]. All the other studies of SAH that mention brain AVMs as a cause have been hospital-based, and mostly retrospective. There seems to be variation between geographical regions and ethnic groups [Becker 1998]; it is debated whether brain AVMs are more common than aneurysms as a cause of SAH in Asian populations, on the basis of studies which do not meet my inclusion criteria [Chee and Loh 1988].

2.3.1.2.5 Epilepsy

Despite the frequency of epileptic seizures, there have been few prospective, community-based studies of people with newly diagnosed epilepsy in the general population [Sander *et al.* 1990]. The estimation of the true frequency of epilepsy is complicated by the difficulty of achieving comprehensive case ascertainment and the heterogeneity of different diseases causing epilepsy. The contribution made by brain AVMs is often hidden by the investigators' classification of aetiologies into broad categories. Furthermore, the extent and frequency of investigation with neuroimaging have been variable between studies, so structural causes – such as brain AVMs – have not always been identified reliably. The use of neuroimaging, ideally MRI, is indicated for patients whose epilepsy cannot be controlled with first-line anti-epileptic drugs, and those with focal epilepsies or fixed/progressive neurological deficits [Duncan 1997], particularly for the identification of brain AVMs. The best information about brain AVMs as a cause of epilepsy in the general adult population comes from a Swedish prospective, population-based incidence study of first presentations with seizures. Using either CT or MRI in all patients, the study found 0.9% (95%CI 0.2 to 5.1) of apparently unprovoked seizures to be attributable to a brain AVM [Forsgren 1990].

2.3.1.2.6 Headache

In the general population, brain AVMs are an extremely infrequent cause of headache. Largely because of neurologists' reasonable aversion to unnecessary investigation, studies have not attempted to ascertain the frequency of structural causes of headache syndromes, defined according to the International Headache Society (IHS) criteria, in unselected populations of people with headache and normal neurological examination. Rather, the majority of existing studies have described small, retrospective, selected series of people at tertiary referral centres, mostly using first-generation CT scanners without intravenous contrast, thereby decreasing the chance of detecting an underlying brain AVM. A pooled synthesis of these imaging studies of the frequency of detection of structural brain abnormalities in samples of over 18 people with unspecified headache and no abnormal neurological signs up to 1991 found 0.3% of them (95%CI 0.1 to 0.7) to harbour a brain AVM [Frishberg 1994]. Only 0.07% (95%CI 0.006 to 0.4) of

migraineurs were found to have a brain AVM in similar studies, several of which used MRI [Frishberg 1997].

2.3.1.2.7 HHT and other neurocutaneous disorders

HHT is a generalised vascular dysplasia that manifests itself in the mucocutaneous membranes, lungs, and gastrointestinal tract as well as in the brain where capillary, venous and arteriovenous malformations are found. The prevalence of brain AVMs in people with HHT has been estimated to lie between 4% and 13% [Román *et al.* 1978; Porteous *et al.* 1992]. However, brain AVMs tend to be small in the context of HHT, often involving a direct fistula between a single afferent and efferent vessel, and their detection is particularly dependent on the use of IADSA [Putman *et al.* 1996; Fulbright *et al.* 1998; Willemse *et al.* 2000]. Due to the limited uptake of IADSA in many of the existing studies of HHT, the frequency of brain AVMs is likely to have been underestimated. Interestingly, at least one third of people with HHT may have multiple brain AVMs [Willemse *et al.* 2000], far in excess of the infrequent multiplicity observed in people with sporadic brain AVMs [Willinsky *et al.* 1990]. Despite the higher prevalence of brain AVMs amongst people with HHT, they seem to be asymptomatic more often than sporadic brain AVMs, which may be an artefact because they are deliberately screened for. In fact, two thirds of any neurological complications are attributable to pulmonary AVMs and not brain AVMs [Guttmacher *et al.* 1995]. There is a relatively higher prevalence of migrainous aura amongst people with HHT, which suggests over-ascertainment by repeated questioning, embolic phenomena from pulmonary AVMs, or perhaps a real association with brain AVMs [Steele *et al.* 1993].

Occasionally, single or multiple brain AVMs occur in the context of two other rare neurocutaneous disorders, usually diagnosed in childhood. In Wyburn-Mason syndrome AVMs affect not only the brain, but also the orbit and face, and in the blue rubber bleb naevus syndrome AVMs also occur in the kidneys and lungs [Kim *et al.* 1998; Fernandes *et al.* 1999].

2.3.2 *Clinical presentation*

Most studies describing the clinical presentation of brain AVMs share many of the methodological failings of studies of their frequency; their small, retrospective nature often leaves uncertainty about the presentation of every person, either because of the lack of radiological investigation, or incomplete data collection. In addition, 'presentation' has been variously interpreted as the clinical event that led to the diagnosis of a brain AVM, or the first symptom in someone's lifetime that was attributable to the brain AVM. Probably in an attempt to estimate the frequency of particular symptoms amongst people with brain AVMs, more than one mode of presentation has tended to be allocated to each individual; for example, the occurrence of seizures and headache with acute ICrH. Furthermore, the roles that brain AVMs play in the aetiology of headache, dizziness and cognitive dysfunction are subject to varying interpretation, resulting in some clinicians attributing the symptoms to the brain AVM, and others declaring the brain AVM asymptomatic, and so incidental.

2.3.2.1 How do brain AVMs present clinically?

Despite these limitations, some general comments can be made about three studies (Figure 9, page 93). Although the sample size was small and the data were collected retrospectively, I have included the population-based study from Olmsted County [Brown, Jr. *et al.* 1996a], but not the study from the Dutch Antilles because of the limitations of its sources of case ascertainment. The only large, multidisciplinary hospital-based studies that allocated a single mode of presentation to each individual and did not have a treatment selection bias (which was either declared in the text, or was implicit in the focus of the paper and the interests of the authors), originate from England [Crawford *et al.* 1986a] and the USA [Mast *et al.* 1997].

The study in Olmsted County provides the most reliable population-based data on the clinical events that led to the diagnosis of a brain AVM, although the small sample size resulted in large confidence intervals around every estimate, and headache, FND and rarer modes of presentation were not mentioned [Brown, Jr. *et al.* 1996a]. Whilst 15% of people harbouring brain AVMs were asymptomatic, and seizures affected 20%, ICrH was the predominant mode of presentation in 65% of the sample.

The two hospital-based series portray different patterns from the population-based study, especially in the proportion of people who are declared asymptomatic (Figure 9, page 93). Many of the differences are likely to have arisen from some of the biases inherent in hospital-based studies. For example, some people may never reach tertiary referral centres, either because they have died or because their symptoms are not thought to merit referral, and others may be referred only because of the availability of a particular treatment. Not only are there differences between population-based and hospital-based series, but large differences have also been demonstrated *between* three hospital-based series in the relative frequencies of different modes of presentation, age at presentation and brain AVM angioarchitecture [Hofmeister *et al.* 2000]. In general, however, the ratio of males to females appears equal, and the mean age at presentation is approximately 35 years, with a standard deviation of approximately 15 years.

2.3.2.2 Which characteristics of brain AVMs are associated with the different modes of presentation?

Because characteristic manners of clinical presentation might help to raise the suspicion of an underlying brain AVM, leading to appropriate investigations, there has been more interest in potential distinguishing features of each mode of presentation than in an accurate appreciation of their relative frequencies. Furthermore, in an effort to gain a quick understanding of why brain AVMs express themselves differently, some of the hospital-based studies have also sought angioarchitectural features that are *associated* with a particular mode of presentation, sometimes making the further inference that these factors are *causative*. Almost all studies of this nature have involved a retrospective correlation of angioarchitecture described *after* diagnosis, with *prior* presentation with ICrH or epilepsy. Although many of these studies have used univariate and multivariate analysis, no amount of statistical sophistication can overcome tenuous cause and effect assumptions.

There are many potential flaws in this attempt to elucidate why some brain AVMs present with haemorrhage, some present with epilepsy and others never cause any symptoms at all. There is not only speculation about how repeated modification of angioarchitecture through life eventually determines clinical presentation, but also good evidence that the angioarchitecture of a brain AVM changes in both the short- and

long-term *after* vessel rupture [Stein and Wolpert 1980; Brown, Jr. *et al.* 1988; London and Enzmann 1981]. The mere occurrence of ICrH may distort angioarchitecture so that any factors found in association with ICrH could be a consequence rather than a cause of it. For example, the interpretation of whether a brain AVM or an associated aneurysm is the cause of haemorrhage can be difficult, with pure SAH around the aneurysm being the principal argument in favour of the aneurysm being responsible [Barracough 1982; Redekop *et al.* 1998]. The occurrence of pseudoaneurysms (an artefact of haemorrhage) on distal feeding arteries and within the nidus in the presence of SAH may lead to their over-interpretation as the cause, but the only way to know for sure is pathological examination or comparison with any prior IADSA [Garcia-Monaco *et al.* 1993; Redekop *et al.* 1998].

Factors associated with the first *occurrence* of ICrH or epilepsy might be spurious for not only these reasons, but also they could be very different from those conferring a higher risk of *recurrence*. This latter risk is what is really of interest to someone with a brain AVM that has bled, and in any discussion of treatment. A particular feature of brain AVMs may be so prevalent in those with one type of presentation, such as ICrH, that it is useless for predicting future events if hospital-based series of mainly ruptured brain AVMs are studied. For example, a study of the first occurrence of seizures found presentation with haemorrhage to be a predictive factor, yet 86% of the cohort had presented in this fashion [Crawford *et al.* 1986b]. This perception may also lead to bias due to the expectation of finding the feature in those with a first occurrence, or recurrence, of haemorrhage. For example, brain AVMs that present with haemorrhage on the whole are smaller and have fewer draining veins than those with other clinical features. These features may be difficult to disentangle as predictors of recurrent haemorrhage, all the more so when cohorts subject to treatment selection bias (usually favouring small brain AVMs) are used to study prognosis.

Where appropriate, I have summarised the findings of studies involving at least 100 people using this flawed retrospective approach as they are useful for identifying putative factors that *might* predict the occurrence, or recurrence, of a particular symptom.

2.3.2.2.1 Haemorrhage

Before the advent of non-invasive imaging of the brain, ICrH from brain AVMs was underestimated because the only possible means for its detection in life was examination of the cerebrospinal fluid (and lumbar puncture would understandably have been avoided in many such cases). Therefore, when ICrH was detected, it was excessively attributed to SAH, so the site of rupture was thought to be predominantly into the subarachnoid space. With or without subarachnoid or intraventricular extension, primary ICeH is now known to be the principal type of haemorrhagic presentation. In the Olmsted County study, primary ICeH accounted for 41%, SAH for 24%, intraventricular haemorrhage for 12% and a combination of these types accounted for 23% of all haemorrhages [Brown, Jr. *et al.* 1996a].

Hospital-based studies retrospectively comparing the angioarchitecture of brain AVMs with a prior haemorrhagic presentation to those with other initial manifestations have identified several factors that seem to be consistently associated with haemorrhage (Table 5, page 86): deep venous drainage, a single draining vein, and venous stenosis. Studies have been more inconsistent about intranidal aneurysms, small nidus size, deep location of the nidus and venous reflux being associated with haemorrhagic presentation. Some studies have identified systemic hypertension and vertebrobasilar or perforating artery supply in association with haemorrhagic presentation [Langer *et al.* 1998; Turjman *et al.* 1995b], but these remain unconfirmed by others. Increasing age at presentation [Langer *et al.* 1998] and smoking [Langer *et al.* 1998; Taha *et al.* 1982] have not been confirmed as associated factors. Potential protective factors that have been investigated are arterial stenosis and ectasia [Mansmann *et al.* 2000], dural arterial supply [Langer *et al.* 1998], venous recruitment [Nataf *et al.* 1998], and angiogenesis [Mansmann *et al.* 2000].

Of course, many of these factors may confound each other; for example, small brain AVMs tend to have only one draining vein and higher feeding mean arterial pressure (FMAP) [Shi *et al.* 1993; Albert *et al.* 1990]. Furthermore, small brain AVMs may present with haemorrhage because they rarely present with epilepsy or other neurological symptoms before diagnosis [Crawford *et al.* 1986a; Brown, Jr. *et al.* 1988], and deeply located brain AVMs tend to be supplied by perforating arteries or the vertebrobasilar system [Turjman *et al.* 1995b].

The consistent findings of a single draining vein, deep venous drainage, venous stenosis and high FMAP being associated with a haemorrhagic presentation may reflect the haemodynamics of these brain AVMs, and suggest that high intranidal pressure may be the major determinant of brain AVM rupture [Hademenos and Massoud 1996]. However, just because these factors are associated with a haemorrhagic *presentation* does not necessarily mean they are also *predictors* of either the occurrence or recurrence haemorrhage. This has to be tested in large, prospective studies.

2.3.2.2.2 Epilepsy

Although their relative frequencies are not described in potentially unbiased samples, epileptogenic brain AVMs clearly can express themselves as apparently generalised seizures, as well as by simple or complex partial seizures with or without secondary generalisation [Miserocchi *et al.* 1984; Osipov *et al.* 1997]. A few studies have examined factors that are retrospectively associated with a presentation with epilepsy. Unsurprisingly, they have found the brain AVMs to have statistically significant associations with a larger (>6cm) nidus diameter [Crawford *et al.* 1986b], and that several other factors (which may well confound each other) seem to be associated including supratentorial cortical location, feeders from the middle cerebral artery, cortical feeders, venous varix, the absence of intranidal aneurysms [Turjman *et al.* 1995a], and location in an arterial borderzone [Stapf *et al.* 2000b]. These factors too should be tested for their prognostic value for the occurrence or recurrence of seizures in long-term, prospective studies.

2.3.2.2.3 Headache

There has been more curiosity and controversy about the semeiology of headache, especially migraine and cluster headache, amongst patients known to have brain AVMs than there has been about how often brain AVMs are a cause of headache in the general population. Again, the absence of prospective, population-based studies with a validation of headache diagnosis has generated conflicting opinions about whether the relationship between headache and brain AVMs is no more than coincidental [Ozer *et al.* 1964; Mohr 1984], in which case the brain AVMs may be dubbed asymptomatic, or

whether there is a greater than chance association [Bruyn 1984; Pereira Monteiro *et al.* 1993].

Publication bias is most likely to explain the reporting of atypical migraine and cluster headache in brain AVM patients, as unusual cases are more likely to be reported in the literature. The migraines reported to accompany brain AVMs are usually characterised by atypical features, although these are not specific for identifying an underlying brain AVM in a person with migraine [Troost and Newton 1975]. The reported headaches tend always to be on the same side, ipsilateral to the brain AVM, with disruption of the classical migraine tempo and sequence [Troost *et al.* 1979; Pereira Monteiro *et al.* 1993; Bruyn 1984; Lees 1962; Frishberg 1994].

A large, prospective cohort study using semi-structured interviews and/or validated questionnaires based on the IHS criteria would be required to determine the true prevalence of different types of headache amongst people with brain AVMs. Studying the converse, the prevalence of brain AVMs amongst patients with various headache syndromes, would be a huge undertaking.

2.3.2.2.4 Focal neurological deficit

Rarely, brain AVMs may cause focal symptoms and signs in the absence of prior or concomitant ICrH. These deficits often have an insidious onset, and their subsequent course may be transient, persistent or infrequently progressive. Occasionally they give rise to fluctuations and slow progression suggesting the diagnosis of multiple sclerosis [Stahl *et al.* 1980]. Their exact frequency in the population is unknown, but they account for up to 10% of presentations in hospital-based series [Crawford *et al.* 1986a; Mast *et al.* 1995; Mast *et al.* 1997]. Whilst these deficits have traditionally been attributed to reduced perfusion pressure (steal) due to high flow in the feeding arteries of the brain AVM, the actual measurement of feeding artery pressures and flow velocities in selected patients has not supported this [Mast *et al.* 1995].

2.3.2.2.5 Cognitive dysfunction

Despite early suggestions that cognitive disorders affect up to 50% of people with brain AVMs [Olivecrona and Riives 1948], there are few data on their frequency amongst

people harbouring brain AVMs; rather, case reports of unusual syndromes and studies of the neuropsychological outcome following treatment populate the literature. Existing research does, however, shed some light on the time of onset of cognitive dysfunction, and the areas of the brain implicated.

Although adults diagnosed with brain AVMs seem to have met their developmental milestones during childhood, a single, retrospective case-control study found that 44 patients affected by brain AVMs were more likely to have had a disorder of learning or behaviour during their school years [Lazar *et al.* 1999]. Subsequent psychological impairments that develop in relation to unruptured brain AVMs do not appear to be equivalent to those from other focal lesions of similar size, nor do they appear to be related just to the area or side of the brain in which the AVM resides [Waltimo and Putkonen 1974; Lazar *et al.* 1997; Brown *et al.* 1989]. Controversial explanations for cognitive deficits related to areas of the brain distant from an AVM are steal – although this is as yet unproven – and venous hypertension [Mahalick *et al.* 1991; Mast *et al.* 1995].

2.3.2.2.6 Other complications

Although pulsatile tinnitus is a celebrated feature of brain AVMs, in particular those within the dura mater, it is in fact unusual [Sabra 1959]. On the limited evidence available, it is a symptom with poor specificity, but which certainly merits at least auscultation over the orbit and cranium, and probably non-invasive investigation [Dietz *et al.* 1994; Waldvogel *et al.* 1998]. Raised intracranial pressure is another infrequent manifestation of brain AVMs, resulting from cerebrospinal fluid outflow obstruction by an enlarged draining vein, or the haemodynamic effect of venous hypertension leading to poor cerebrospinal fluid resorption [U and Kerber 1983; Chimowitz *et al.* 1990]. Of course, other deficits depend on the location and size of a brain AVM, so those in the occipital lobes may cause atypical visual disturbance [Maleki and Kirkham 1983], those in the posterior fossa can cause cranial nerve palsies [Hatori *et al.* 1991], trigeminal neuralgia [Johnson and Salmon 1968] and hemifacial spasm [Kim *et al.* 1991], whilst movement disorders can be caused by AVMs of the basal ganglia [Lobo-Antunes *et al.* 1974].

2.3.2.2.7 Health-related quality of life

Whilst only one published study of untreated brain AVMs has used validated self-reported measures of disability [Hartmann *et al.* 1998], there has also been only one study of people affected by brain AVMs to explore their perceptions of health and risks for the future. A small study, using the standard gamble technique to compare patients' different health states by the utility values they assigned to them, demonstrated considerable variation in individuals' perceptions of their quality of life [Shin *et al.* 1997]. This clearly suggests that patients should be involved in decision-making about their own management, as their future quality of life is affected not only by their prognosis, but also by their interpretation of it. Larger studies are needed to evaluate the factors associated with patients' different perceptions of their health, especially in the context of their treatment and the design of clinical trials.

2.3.3 Prognosis

2.3.3.1 Methodological problems with studies of brain AVM prognosis

Once again, ideal study design (Table 4, page 85) has been approached by very few of the existing observational cohort studies, leading to varying degrees of bias. I have therefore chosen the studies that best meet my requirements, explicitly mentioning their failings in particular areas (Table 6, page 87).

Definitions of the diagnostic criteria for a brain AVM or its angioarchitectural features and information about the extent of investigation to achieve adequate diagnostic certainty are provided so infrequently that I have not rejected any studies on these criteria alone. Some studies have used restrictive entry criteria (including only those patients with 'adequate' imaging and complete data collection) to produce a more homogeneous cohort, although this inevitably results in a more selective cohort. Furthermore, many of the older studies enrolled patients before the modern era of brain imaging [Graf *et al.* 1983; Crawford *et al.* 1986a]. Because there is only one truly population-based study, I have not rejected any study solely on the grounds of being hospital-based, but the fact that they are all likely to suffer selection bias should not be

ignored. Retrospective survival cohorts far outweigh studies with a prospective design, mainly because large amounts of data are available immediately, but the data are, by their nature, incomplete and inaccurate.

The inception point has been unclear in many studies. The uncertainty about exactly when a brain AVM develops, and its evolution during the latent period of 'maturation' before clinical presentation, surely make a 'lifetime' period of risk with inception at birth an invalid assumption, involving by its nature a retrospective assessment of the clinical course [Martin *et al.* 1995]. The inclusion of this latent period in the denominator of the calculation of time at risk attenuates the apparent annual risk of an outcome. Moreover, the prognosis from the point of diagnosis onwards is what concerns patients and clinicians alike, especially from the point of view of treatment.

Follow-up has been variable both in duration and completeness. Scarcely any studies have achieved more than 10 years of follow-up. In retrospective studies, completeness has been quoted as near 100%, but I have already discussed the vagaries of this method of data collection. In prospective studies, the completeness of follow-up has been more variable, having potentially dramatic effects on less frequent outcomes in particular. The assessment of outcome has never been blinded to features of the people under study that are hypothesised to determine prognosis, and has often lacked standardisation with authors frequently adopting their own arbitrary outcome scales. Outcome has usually been assessed at varying time intervals, often without actuarial analysis, and without stratification by differences in treatment after inception, making comparison of different cohorts virtually impossible.

Again, I have been careful to include only the largest series from each research group, because existing series have been republished, either when they have enlarged, or after further follow-up [Ondra *et al.* 1990; Troupp 1965; Troupp *et al.* 1970].

A meta-analysis of the included studies has not been possible because comparable outcomes cannot be derived from them, they have poor generalisability due to variations in confounding effect modifiers, and there are likely to be different selection biases operating at specialist treatment centres [Egger *et al.* 1998]. In any attempted quantitative synthesis, the heterogeneous biases of these studies would be combined rather than diluted in a pooled estimate and I would be, "simply producing tight

confidence intervals around spurious results” [Egger *et al.* 1998; Egger *et al.* 2001]. Instead, I have tabulated the best available evidence (Table 7 to Table 9, pages 88-90).

2.3.3.2 What is the risk of death?

Detailed information about the early and long-term risk of death for people with a brain AVM is sparse (Table 7, page 88). Because there are no long-term population-based data on the risk of death following the diagnosis of a brain AVM, the brain AVM ‘mortality rate’ (number of deaths per 1000 per unit time) is unknown. Studies only yield information about the proportion of people with a brain AVM who die (the ‘case fatality’).

People with a haemorrhagic presentation do appear to have a lower case fatality compared to other causes of primary ICeH and aneurysm rupture [Perret and Nishioka 1966; Rosenow *et al.* 1997]. In the Olmsted County study [Brown, Jr. *et al.* 1996a], the 30 day case fatality following a first ICeH from a brain AVM was 18% (95%CI 4% to 43%). Presumably because of selection bias, in hospital-based survival cohorts case fatality following ICeH has ranged from 0% over approximately one year in recent studies [Hartmann *et al.* 1998; Mast *et al.* 1997], to 17% over at least one year following an initial or recurrent ICeH in another [Porter *et al.* 1998]. Interestingly this does not seem to translate into a long-term difference in survival between patients presenting with and without ICeH. Long-term crude annual case fatality rates appear to lie between 1% and 1.5% per annum, with no factors apparently conferring a greater risk of death, although 50% to 70% of all deaths are due to ICeH [Crawford *et al.* 1986a; Ondra *et al.* 1990].

2.3.3.3 What is the risk of developing intracranial haemorrhage?

Because ICeH is the most feared outcome of a brain AVM, there has been an overwhelming curiosity about the frequency and risk of its occurrence and recurrence, and a tendency to treat brain AVMs early in an attempt to avoid it. The crude annual rate of ICeH from brain AVMs is widely quoted to be approximately 2% in the existing hospital-based studies of prognosis (Table 8, page 89), although this must mask important variations in the behaviour of different subgroups.

2.3.3.3.1 First-ever haemorrhage

From the few studies of the clinical course of unruptured brain AVMs, the crude annual risk of a first-ever ICrH appears to be approximately 2% [Brown, Jr. *et al.* 1988; Mast *et al.* 1997]. Whilst one study found no factors that predicted the occurrence of ICrH [Brown, Jr. *et al.* 1988], a sub-study of the same patient group with complete IADSA examinations found the co-existence of aneurysms at baseline conferred a higher annual rate of first-ever ICrH for people with unruptured brain AVMs [Brown, Jr. *et al.* 1990].

2.3.3.3.2 Recurrent haemorrhage

Because the majority of brain AVMs present with ICrH, their risk of recurrent ICrH has been studied more often than the risk of its first-ever occurrence. Early treatment following ICrH may, of course, preclude the study of the real natural history of its recurrence. People who have already experienced ICrH are thought to carry a risk of recurrence greater than the 2% annual risk of first-ever occurrence, possibly up to 18% in the first year [Mast *et al.* 1997]. Some studies have found the risk of recurrent ICrH after a haemorrhagic presentation to be greater than the risk of first-ever ICrH after any other type of presentation [Crawford *et al.* 1986a; Mast *et al.* 1997], whilst other methodologically less sound studies have not [Graf *et al.* 1983; Ondra *et al.* 1990]. These studies have found other features to predict recurrence of ICrH, including exclusively deep venous drainage and male sex [Mast *et al.* 1997], increasing age [Crawford *et al.* 1986a], and small nidus size [Graf *et al.* 1983], although the studies are not all in agreement (Table 8, page 89). None of these factors predictive of recurrence were identified by a celebrated long-term prospective study that found a 4% crude annual risk of ICrH [Ondra *et al.* 1990]. This study was, however, flawed in some respects. It enrolled patients before the modern era of neuro-imaging, making the diagnosis of ICrH potentially inaccurate; by being based at a specialist centre, although serving most of its country, it was only more-or-less population-based; and it calculated bleeding rates in 5-year intervals, without an actuarial analysis, potentially masking a short-term higher risk of recurrence.

2.3.3.3 Morbidity caused by haemorrhage

The recognition of a lower case fatality in comparison to other causes of ICrH has generated further interest in the morbidity attributable to haemorrhage caused by brain AVMs (Table 8, page 89). Theoretically, the morbidity of brain AVM rupture may be ameliorated by patients being younger than their counterparts with primary ICeH, by haemorrhage occurring from vessels at a lower pressure than aneurysmal SAH or spontaneous primary ICeH, by there being less vasospasm than after aneurysmal SAH [Sasaki *et al.* 1981], and by the limitation of haemorrhage to the nidus of the brain AVM. Furthermore, the morbidity of ICrH may be less than previously thought, perhaps because the improved resolution and availability of non-invasive imaging have augmented the detection of small primary ICeH. In a recent study, up to 84% of patients with a first occurrence of haemorrhage made a full recovery or scored only 1 on the Rankin scale [Hartmann *et al.* 1998], whilst in another only 45% made a recovery without a permanent deficit [Porter *et al.* 1998]. These findings were, however, based on hospital-based survival cohorts, and are probably subject to their inherent biases, in particular that people who were more disabled at presentation may not have been ascertained. Whether recurrent ICrH carries a similar morbidity is even less certain [Hartmann *et al.* 1998; Porter *et al.* 1998].

2.3.3.4 Prediction models

Prognostic models are useful for helping to make informed decisions in routine clinical practice, in particular for deciding who may be at greatest risk with conservative management. However, in the absence of a relatively uniform consensus on the important prognostic factors for patients with brain AVMs, the generalisability of the conflicting results of the existing multivariate analyses is poor. In an effort to simplify the issue of risk prediction, a general 2-4% annual risk of (first or recurrent) ICrH has been used to determine the likelihood of survival free of ICrH using the multiplicative law of probability [Kondziolka *et al.* 1995; Brown, Jr. and Kondziolka 2000]. However, these calculations assume population homogeneity and a uniform risk of ICrH over time, both of which are very unlikely to be the case.

2.3.3.4 What is the risk of developing seizures?

Little attention has been given to the risk of epilepsy from brain AVMs (Table 9, page 90), especially by authors who thought that seizure disorders, although common, were too difficult to quantify [Ondra *et al.* 1990]! From the data that are available, it appears that people with brain AVMs carry an annual risk of developing *de novo* seizures of 1%, and they may be at a greater risk following presentation with haemorrhage, or if they are older [Crawford *et al.* 1986b]. However, when they do occur, at least three quarters of patients' seizures come under good control on first line anti-epileptic drugs [Osipov *et al.* 1997].

2.3.3.5 Pregnancy

Controversy has dogged the influence that pregnancy, labour, different modes of delivery and the puerperium may have on bleeding rates from brain AVMs. Some women with brain AVMs are advised against pregnancy, others are sterilised, and those who do become pregnant may or may not be encouraged to have a Caesarean section or a termination [Horton *et al.* 1990; Velut *et al.* 2000]. One retrospective study of women of childbearing age in an untreated survival cohort being considered for stereotactic radiosurgery, without information on the completeness of follow-up or a statistical analysis, compared their crude rates of first or recurrent haemorrhage outwith and during pregnancy [Forster *et al.* 1993]. Compared to the bleeding rate of 4.5% per annum when they were not pregnant, there was a higher rate of haemorrhage during the second trimester (17% per annum), but not in the other stages of gestation. A second similar study found no influence of pregnancy on haemorrhage rates, although its conclusions are invalidated in a sensitivity analysis by changing the arbitrary duration of pregnancy that they chose [Horton *et al.* 1990].

Of course, there are several biases inherent in these studies; in particular, the occurrence of haemorrhage may have a fatal outcome so preventing future pregnancy, or discourage some women from becoming pregnant if the haemorrhage is not fatal. Although it is logistically difficult to resolve this dilemma, only a population-based, prospective cohort study could examine pregnancy as a risk factor for the development of haemorrhage.

2.3.3.6 Hereditary haemorrhagic telangiectasia

Despite the prevalence of brain AVMs in people with HHT, there is a paucity of information about their prognosis, and whether it is any different from sporadic brain AVMs. AVMs of the brain were an infrequent cause of death in a population-based study of people with HHT [Kjeldsen *et al.* 1999]. A small study in which a large proportion of people were asymptomatic, with a short prospective follow-up period in which no haemorrhages were observed, suggested that the risk of ICH from a brain AVM in the context of HHT may be lower than for people with sporadic brain AVMs, based on an annual bleeding rate of 0.4% (95%CI 0.1% to 1.2%) derived from a lifetime-risk assumption. Clearly, here too large prospective, population-based studies are needed.

2.4 Summary

- There is a serious shortage of high quality studies of the frequency, presentation, clinical course and prognosis of brain AVMs
- Whilst very little can be reliably concluded about the likely prevalence of brain AVMs, their incidence in unselected populations is of the order of 1 per 100,000 per year
- Long-term crude annual case fatality due to a brain AVM is 1-1.5%
- The crude annual risk for the first occurrence of a haemorrhage from an unruptured brain AVM is approximately 2%, and this may be increased by co-existent aneurysm(s)
- The risk of haemorrhage recurrence may be as high as 18% in the first year, although consistent risk factors for haemorrhage recurrence have not yet been observed
- Brain AVMs seem to carry an annual risk of developing *de novo* seizures of 1%, with a good prospect of control on anti-epileptic drugs
- The risk of rupture during pregnancy and for patients with HHT has not been accurately established

2.5 Discussion

Many of the existing studies of their frequency have not met my selection criteria, or the studies are no longer appropriate because of the radical improvements in imaging of the brain's vasculature over the last two decades. A clear brain AVM definition was lacking in so many of the studies I have selected that if I had excluded any of them on this criterion alone, there would have been hardly any left. Clearly, there is still a need for some large, prospective studies of the incidence and prevalence of brain AVMs in well-defined, stable populations across the world, with widespread availability and uptake of CT, MRI and IADSA.

Despite the large number of studies of the clinical course of brain AVMs, very few meet rudimentary standards for an ideal design, and fewer still provide consistent results that can be extrapolated to the generality of people with brain AVMs. It is, of course, difficult to assess the clinical course of brain AVMs because of their heterogeneity and because they are often treated when discovered.

Because of the inconclusive and uncertain nature of existing research about the clinical course of brain AVMs, clinicians are frequently faced with various management dilemmas: what is the clinical course of brain AVMs in general, what is the prognosis for a particular person, and which treatment(s) – if any – should be used?

There is therefore a pressing need for prospective, population-based observational cohort studies of people with brain AVMs, both ruptured and unruptured. These studies should share core methods (Table 4, page 85) in order to minimise both bias and confounding to an acceptable level, to make studies comparable, and to speed the evaluation of prognosis with the greatest world-wide economy of research effort by cautiously synthesising their results [Sudlow and Warlow 1996; Sackett *et al.* 1991; Al-Shahi and Warlow 2001]. They may help to elucidate the untreated clinical course for large groups of people with brain AVMs (mortality rate, case fatality, and prognosis for first or recurrent haemorrhage or seizures), and the factors that determine prognosis for particular individuals. The widespread availability and uptake of brain imaging now provide a timely opportunity to address many of these unanswered questions about brain AVMs.

Even with thorough, targeted investigation of their presenting symptoms, the number of patients will still be comparatively small. Therefore, multicentre studies, possibly with international collaboration, will be required to collect sufficient people with untreated brain AVMs to prospectively establish their clinical course over several decades.

Whilst these people may be subject to treatment selection bias, current variation in practice – reflecting uncertainty about whether and how to treat brain AVMs – will eventually mean that a representative sample is collected. In the interim, these studies will generate useful observational data about both beneficial and adverse effects of treatment, which may lead to appropriate randomised trials. Although these trials will be difficult to do, and will clearly require multicentre collaboration, they are particularly necessary in the context of a condition where the prognosis is uncertain for groups of people, let alone for any particular individual.

But it is likely that the true natural history of brain AVMs – be it identical to or different from existing knowledge – will be the last uncertainty to be resolved. In the next section I describe and evaluate the design of a prospective, population-based cohort study of newly diagnosed brain AVMs in adults – the Scottish Intracranial Vascular Malformation Study (SIVMS) – which I set up in 1998 to address this uncertainty.

Table 2 Electronic literature search strategies

Ovid Medline on Biomedical Data Services from 1966 to February 2001

Line number	Search term
1	exp cerebral arteries/
2	exp cerebral arterial diseases/ or intracranial arterial diseases/
3	cerebral veins/
4	exp cerebral ventricles/
5	(cranial or cerebral or cerebell\$ or brain\$ or dural or supratentorial or intracerebral).tw
6	1 or 2 or 3 or 4 or 5
7	arteriovenous malformations/ or arteriovenous fistula/
8	angioma\$.tw
9	((arteriovenous or vascular) adj10 malformation\$).tw
10	7 or 8 or 9
11	6 and 10
12	cerebrovascular malformation\$.tw
13	intracranial arteriovenous malformations/
14	11 or 12 or 13
15	limit 14 to human

EMBASE from Bath Information Data Services from 1980 to February 2001

Line number	Search term
1	exp brain artery/
2	cerebrovascular disease/
3	brain vein/
4	exp brain ventricle/
5	(cranial or cerebral or cerebell\$ or brain\$ or dural or supratentorial or intracerebral).tw
6	1 or 2 or 3 or 4 or 5
7	arteriovenous malformation/
8	angioma\$.tw
9	((arteriovenous or vascular) adj10 malformation\$).tw
10	7 or 8 or 9
11	6 and 10
12	cerebrovascular malformation\$.tw
13	brain arteriovenous malformation/ or cerebrovascular malformation/
14	11 or 12 or 13
15	limit 14 to human

Table 3 Literature search sensitivity and precision

Sensitivity = (articles identified by literature search / articles identified by hand search)

Precision = (relevant articles identified by literature search / all articles identified by literature search in *AJNR* and *J Neurosurgery* 1986 and 1996) = $34/79 = 43\%$

	Year	Literature search	Hand search	Sensitivity (%)	95%CI
<i>AJNR</i>	1986	3	5	60	17-100
	1996	6	7	86	60-100
<i>J Neurosurgery</i>	1986	8	8	100	-
	1996	16	16	100	-
Overall		34	36	94	87-100

Table 4 Characteristics of the ideal study of brain AVM prognosis

Diagnostic certainty at baseline

Inception cohort

Prospective data collection

Population-based sample

Sample size ≥ 100

Objective, pre-defined outcome events and validated measures of functional status

Assessment of outcome blinded to baseline factors of interest

Stratification of outcome by differences in treatment

Follow-up $\geq 90\%$ complete

≥ 5 year follow-up

5 year survival rate and an actuarial analysis of the chosen outcomes

Table 5 Angioarchitectural features of brain AVMs associated with a *prior* haemorrhagic presentation in retrospective studies

Factor	Statistically significant ($p < 0.05$) association found	No association found
Deep venous drainage	Duong <i>et al.</i> 1998 Langer <i>et al.</i> 1998 Nataf <i>et al.</i> 1998 Turjman <i>et al.</i> 1995b Kader <i>et al.</i> 1994 Miyasaka <i>et al.</i> 1992	
Single draining vein	Shi <i>et al.</i> 1993 Miyasaka <i>et al.</i> 1992 Albert <i>et al.</i> 1990	
Venous stenosis	Nataf <i>et al.</i> 1998 Mansmann <i>et al.</i> 2000 Miyasaka <i>et al.</i> 1992	
High feeding mean arterial pressure	Duong <i>et al.</i> 1998	
Intranidal aneurysm	Redekop <i>et al.</i> 1998 Nataf <i>et al.</i> 1998 Turjman <i>et al.</i> 1995b	Meisel <i>et al.</i> 2000 Duong <i>et al.</i> 1998 Langer <i>et al.</i> 1998 Mansmann <i>et al.</i> 2000
Small nidus size	Langer <i>et al.</i> 1998 Kader <i>et al.</i> 1994 Shi <i>et al.</i> 1993 Albert <i>et al.</i> 1990 Crawford <i>et al.</i> 1986a Mansmann <i>et al.</i> 2000	Duong <i>et al.</i> 1998
Deep location	Mansmann <i>et al.</i> 2000 Turjman <i>et al.</i> 1995b	Duong <i>et al.</i> 1998 Langer <i>et al.</i> 1998
Venous reflux	Nataf <i>et al.</i> 1998	

Table 6 The extent to which the best studies of prognosis have met my selection criteria

● = criterion was met; ○ = criterion was not met; - = not applicable; ? = unknown

	Diagnostic certainty	Inception cohort	Purely prospective	Population-based	Sample size > 100	Objective outcomes	Blinded assessment of outcome	Stratified by differences in treatment	Follow-up ≥ 90%	> 5 year follow-up	Actuarial analysis
Brown, Jr. <i>et al.</i> 1988	●	●	○	○	●	●	○	●	●	●	●
Brown, Jr. <i>et al.</i> 1990	●	●	○	○	○	●	○	●	●	●	●
Brown, Jr. <i>et al.</i> 1996b	●	●	○	●	○	●	○	○	●	○	○
Crawford <i>et al.</i> 1986a; Crawford <i>et al.</i> 1986b	?	●	○	○	●	●	●	●	○	●	●
Forster <i>et al.</i> 1993	?	○	○	○	●	●	●	●	?	-	●
Graf <i>et al.</i> 1983	●	●	○	○	●	●	○	?	?	●	●
Hartmann <i>et al.</i> 1998	?	●	●	○	●	●	○	-	●	○	-
Horton <i>et al.</i> 1990	●	-	○	○	●	●	○	●	●	-	○
Mast <i>et al.</i> 1997	?	●	●	○	●	●	○	-	●	○	●
Ondra <i>et al.</i> 1990	●	?	○	○	●	●	○	●	●	●	○
Osipov <i>et al.</i> 1997	?	●	●	○	○	●	○	○	●	○	○
Porter <i>et al.</i> 1998	?	●	●	○	●	●	○	?	●	○	○

Table 7 Studies of brain AVM clinical course after first presentation with information about case fatality

Where no overall average period of follow-up is given in the original studies, the range of average follow-up for the subgroups is given

Study details	Patient group	n	Outcome	% dead	Assessed at	Predictors of death
Prospective studies						
Mast <i>et al.</i> 1997	Presentation with haemorrhage (n=142) or other symptoms (n=139)	281	Case fatality	0%	8 to 12 months (mean)	Not applicable
Porter <i>et al.</i> 1998	First haemorrhage at presentation (n=75) or during follow-up (n=56)	131	Case fatality due to haemorrhage	17%	≥ 12 months	Haemorrhage during follow-up
Hartmann <i>et al.</i> 1998	First haemorrhage at presentation (n=115) or during follow-up (n=4)	119	Case fatality	0%	≥ 1 month. 16 months (mean)	Not applicable
Mixed prospective and retrospective studies						
Ondra <i>et al.</i> 1990	Presentation with haemorrhage (n=114) or other symptoms (n=46)	160	Crude annual case fatality (all cause)	1% <i>per annum</i>	24 years (mean)	None discovered
Retrospective studies						
Brown, Jr. <i>et al.</i> 1996b	Presentation with haemorrhage	17	Case fatality	18%	30 days after bleed	None discovered
Crawford <i>et al.</i> 1986a	Presentation with haemorrhage (n=139) or other symptoms (n=78)	217	Crude annual case fatality (all cause)	~1.5% <i>per annum</i>	7 to 10 years (mean)	Location anywhere except the parietal lobe

Table 8 Studies of brain AVM clinical course after first presentation with information about the prognosis for intracranial haemorrhage

Where no overall average period of follow-up is given in the original studies, the range of average follow-up for the subgroups is given

Study details	Patient group	n	Outcome	% with outcome	Assessed at	Outcome predictors
Prospective studies						
Mast <i>et al.</i> 1997	Presentation with haemorrhage (n=142) or other symptoms (n=139)	281	<i>Haemorrhagic presentation</i> Annual re-bleed rate (5 year risk) <i>Other presentations</i> Annual first and recurrent bleed rate (5 year risk)	18% (58%) 2% (10%)	8 to 12 months (mean)	Haemorrhagic presentation, male sex and exclusively deep venous drainage
Porter <i>et al.</i> 1998	First haemorrhage at presentation (n=75) or during follow-up (n=56)	131	Recovery Permanent deficit	45% 38%	≥ 12 months	Haemorrhage predicted permanent deficit
Hartmann <i>et al.</i> 1998	First haemorrhage at presentation (n=115) or during follow-up (n=4)	119	Recovery or Rankin 1 Rankin 2-3 Rankin ≥ 4	84% 13% 3%	≥ 1 month. 16 months (mean)	ICeH as opposed to other types of intracranial haemorrhage
Mixed prospective and retrospective studies						
Ondra <i>et al.</i> 1990	Presentation with haemorrhage (n=114) or other symptoms (n=46)	160	Annual bleed rate	4% per annum	24 years (mean)	None discovered
Retrospective studies						
Brown, Jr. <i>et al.</i> 1990	Unruptured AVMs	91	<i>Coexisting aneurysm</i> Annual bleed rate at 5 years <i>No aneurysm</i> Annual bleed rate at 5 years	7% per annum 1.7% per annum	≥ 4 years	Coexistent aneurysm
Crawford <i>et al.</i> 1986a	Presentation with haemorrhage (n=139) or other symptoms (n=78)	217	Annual bleed rate	2% per annum	7 to 10 years (mean)	Haemorrhagic presentation and increasing age
Graf <i>et al.</i> 1983	Presentation with haemorrhage (n=134) or other symptoms (n=57)	191	Annual bleed rate	2% per annum	2 to 5 years (mean)	Small nidus size

Table 9 Studies of brain AVM clinical course *after* first presentation with information about the prognosis for seizures

Study details	Patient group	n	Outcome	% with outcome	Assessed at	Outcome predictors
Mixed prospective and retrospective studies						
Osipov <i>et al.</i> 1997	Presentation with seizures alone	92	Seizure cessation	75%	2 years (median)	None discovered
	(all treated with anticonvulsants)		≤ 1 seizure per year	11%		
			Weekly-monthly seizures	14%		
Retrospective studies						
Crawford <i>et al.</i> 1986b	No prior seizures Presentation with haemorrhage (n=210) or other symptoms (n=35)	245	Annual risk of developing <i>de novo</i> seizures	1% <i>per annum</i>	7 years (median)	Haemorrhagic presentation and increasing age at diagnosis

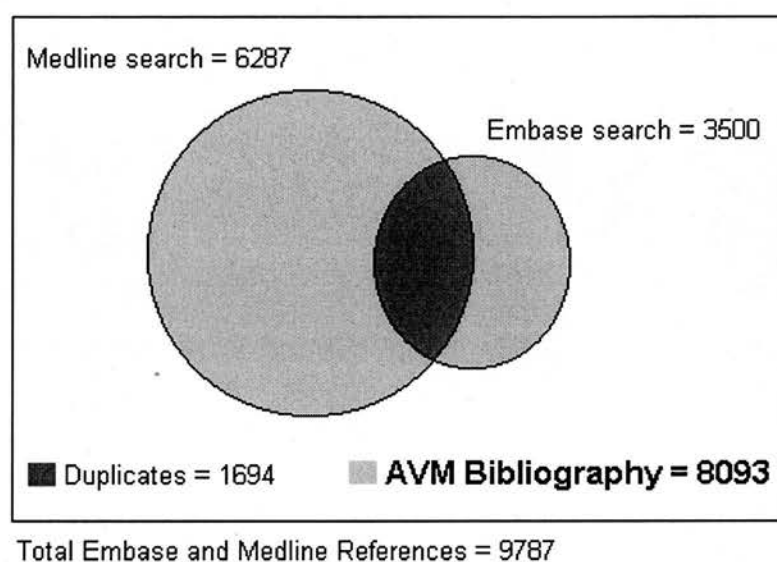
Figure 7 Literature search results

Figure 8 Frequency of brain AVMs in different patient and age groups, with point estimates and 95% confidence intervals

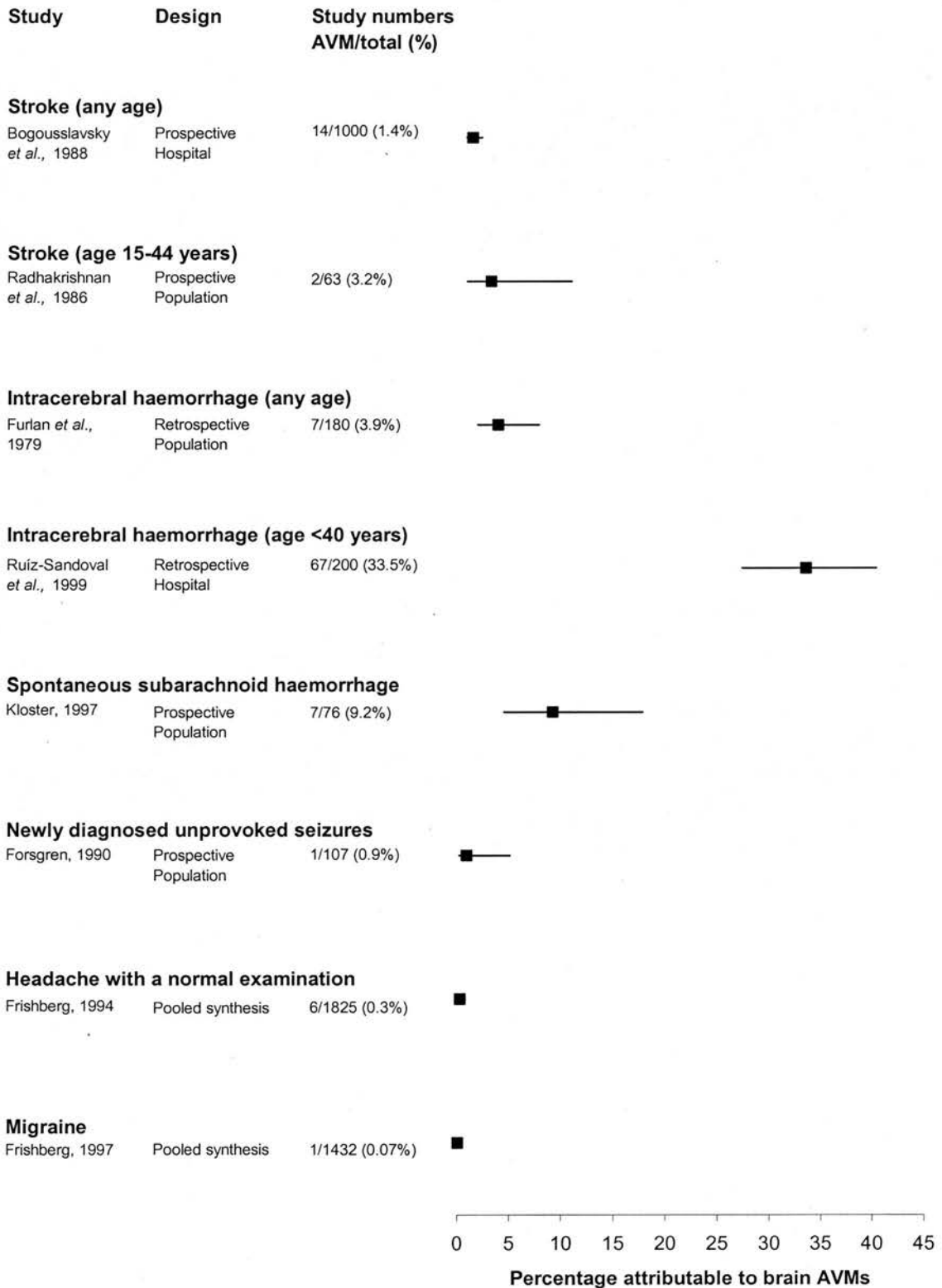
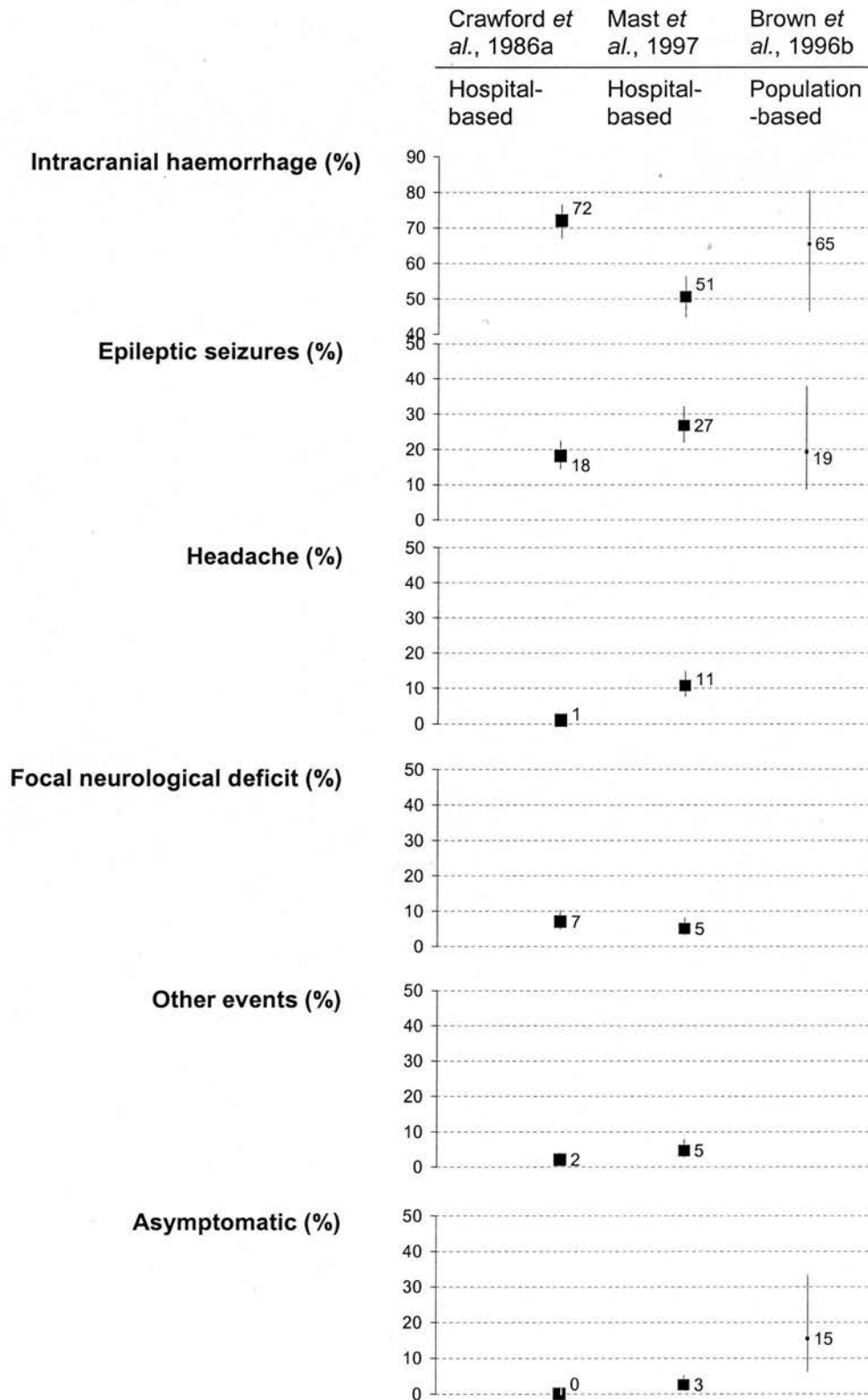


Figure 9 The relative frequencies of clinical events at diagnosis, with point estimates and 95% confidence intervals

Headache, focal neurological deficit and other modes of presentation were not mentioned in Brown et al. 1996b



Section 2: The Scottish Intracranial Vascular Malformation Study (SIVMS) – methods and design

- Chapter 3 Methods of a population-based disease register for adults with intracranial vascular malformations
- Chapter 4 Database design for a population-based disease register for adults with intracranial vascular malformations
- Chapter 5 Variables relating to patients with brain arteriovenous malformations and their clinical features
- Chapter 6 Morphological variables relating to brain arteriovenous malformations

Chapter 3. Methods of a population-based disease register for adults with intracranial vascular malformations

Chapter contents

- 3.1 Introduction
- 3.2 Study design and process
 - 3.2.1 SIVMS inclusion criteria
 - 3.2.2 SIVMS exclusion criteria
 - 3.2.3 Diagnostic criteria specifically for brain AVMs in SIVMS
 - 3.2.3.1 Morphological definition
 - 3.2.3.2 Pathological definition
 - 3.2.3.3 Radiological diagnostic criteria
 - 3.2.3.4 Certainty
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 - 3.2.4.1 Demographics of Scotland
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 - 3.2.7 Notification
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Chapter contents (continued)

- 3.2.10 Collection of study materials during follow-up
 - 3.2.10.1 GP questionnaire
 - 3.2.10.2 Patient questionnaire
 - 3.2.10.3 Medical records
- 3.2.11 Collection of materials when a patient dies
- 3.3 Study audit
- 3.4 Summary
- 3.5 Discussion
 - 3.4.1 Inclusion
 - 3.4.2 Recruitment
 - 3.4.3 Technological enhancements
 - 3.4.4 Comparison with other studies

3.1 Introduction

Because of the inconclusive nature of most of the existing literature about all IVMs – and not just the deficiencies I exposed in the brain AVM literature in Chapter 2 – I set up the Scottish IVM Study (SIVMS) in the autumn of 1998. The study team included myself, an administrator (Rosemary Anderson), my supervisor (Professor Charles Warlow), and a multidisciplinary, collaborative steering committee representative of the four neuroscience centres in Scotland (Chapter 19). Data collection started on 1st January 1999 and will continue uninterrupted until, at the earliest, January 2005. This chapter describes study design, and descriptions of the database and variables follow.

3.2 Study design and process

3.2.1 *SIVMS inclusion criteria*

Patients are provisionally included in SIVMS if they meet the following criteria (according to their data supplied by the source(s) of notification):

-
- Any of the principal sub-types of IVM¹:
 - a) Brain AVM (including brain arteriovenous fistulae)
 - b) Dural AVM (including carotid-cavernous fistulae)
 - c) Cavernous malformation (CM)
 - d) Venous malformation (VM)
 - Date of first-in-a-lifetime diagnosis (by imaging or histology) \geq 1st January 1999
 - Age \geq 16 years at the time of this diagnosis
 - Permanently resident in Scotland at the time of this diagnosis
-

¹ Although SIVMS recruits adults with any type of IVM, this thesis only relates to brain AVMs

After notification, a patient's provisional inclusion is confirmed or refuted following review of case notes, pathology reports and diagnostic brain imaging when they eventually become available (see 3.2.9, page 106). Only adults are included because of the different consent procedures required for children and the different clinical behaviour of brain AVMs in the paediatric population.

Diagnostic criteria for brain AVMs are described below (3.2.3, page 98). Occasionally an included patient may harbour more than one brain AVM (for example, in people with HHT). Intermediate types of IVM arise, with radiological and/or pathological characteristics overlapping different IVM types; the greatest difficulty arises in telling CMs and VMs apart. Whilst these rare, intermediate forms of IVM are 'included', they are never regarded as 'definite' (3.2.3.4, page 99) and form a separate subgroup for analysis.

3.2.2 *SIVMS exclusion criteria*

- Incorrect diagnosis of an IVM
- Other types of intracranial vascular malformation
 - a) Vein of Galen malformation
 - b) Dural AVMs with exclusively spinal medullary venous drainage
 - c) Capillary malformation/telangiectasis
- Spinal vascular malformation

3.2.3 *Diagnostic criteria specifically for brain AVMs in SIVMS*

For the purpose of a generaliseable population-based study, the working definition used by SIVMS to diagnose a brain AVM reflects routine clinical practice by being dependent only on minimum adequate radiological and/or pathological investigations.

3.2.3.1 Morphological definition

A brain AVM is an anastomosis of non-nutritive blood vessels in the brain parenchyma, in which arteriovenous shunting occurs in a nidus (the area towards which usually multiple feeding arteries converge, and from which one or more veins drain). This working definition includes a brain AVF (which involves a single direct fistula between one feeding artery and one draining vein), but excludes pure vein of Galen malformations and dural AVMs.

3.2.3.2 Pathological definition

Macroscopically, a brain AVM is an abnormal tangle in the brain parenchyma composed of tortuous vessels of varying calibre, occasionally calcification, and often thickened and opacified overlying leptomeninges (Figure 3, page 51). Microscopically, a brain AVM is composed of vessels which have a mature phenotype, but which are morphologically between arteries and veins (due to the haemodynamic stresses placed upon them) and intervening capillaries are missing [McCormick 1966].

3.2.3.3 Radiological diagnostic criteria

Brain AVMs may be suggested (but not regarded as definite) by calcification on CT, but they are only definite if the tangle of vessels enhances with contrast [Kumar *et al.* 1984]. Brain AVMs are seen as a serpiginous cluster of flow voids on standard spin-echo MRI (T_1 and T_2), representing multiple dilated vascular channels with relatively rapid blood flow, which usually enhance with contrast (although this is usually not necessary for a definite diagnosis) [Wallace and Bourekas 1998]. Four-vessel IADSA demonstrates the collection of abnormal vessels within the brain parenchyma, associated with early visualisation of veins during the late arterial or capillary phase on rapid sequence angiography.

3.2.3.4 Certainty

It is not always the case that investigations establish a brain AVM diagnosis beyond all doubt. Therefore, a measure of certainty (definite/probable/possible) is attached to the

diagnosis of each brain AVM on every investigation to reflect routine practice. Whilst 'definite' diagnoses meet the diagnostic criteria above, the distinction between 'probable' and 'possible' is more subjective, being based on the clinical instincts of the notifying radiologist/pathologist and the SIVMS neuroradiologists (see Table 10, page 114).

Brain AVM diagnosis may be uncertain on imaging because extensive radiological investigation has not been performed. This may have been because it was thought to be clinically inappropriate, because the patient declined it, or because it was not available (for examples see section 13.3.1, page 257). Even when thorough investigation is undertaken, only a small remnant of AVM may be visualised preventing a definite diagnosis from being made. This usually occurs in two situations following ICrH from a brain AVM. Firstly, a brain AVM may be 'angiographically-occult' due to compression by haematoma, especially in the acute phase of ICeH. Secondly, an IADSA might only demonstrate an early draining vein that would implicate a brain AVM – now with its nidus obliterated by the haemorrhage – as the 'probable' cause; haemodynamic changes or recanalisation might lead to the subsequent appearance of the AVM, whereas spontaneous obliteration/thrombosis might result in its disappearance.

Inevitably, certainty of radiological diagnosis is also affected by variation between observers reflecting their experience and professional perceptions about the interpretation of diagnostic studies of brain AVMs. This will be explored further in Chapter 10.

For these reasons, the final decision about radiological certainty of diagnosis and the collection of detailed angiographic data is taken collectively after review of *all* diagnostic imaging. Certainty is arbitrated at consensus meetings between the SIVMS research fellow (myself 1999-2001) and the two consultant interventional neuroradiologists (Dr Robin J Sellar, Western General Hospital, Edinburgh and Dr Jo J Bhattacharya, Southern General Hospital, Glasgow). If any participant is found to have received an incorrect diagnosis of a brain AVM after review of their CT/MRI/IADSA by the study neuroradiologists, they are excluded.

Certainty of pathological diagnosis is determined from pathologists' reports of autopsies and specimens from surgical excision, and is not subject to independent review.

A patient is not excluded if a brain AVM diagnosis is possible, but its certainty is less than 'definite'. In routine clinical practice, management sometimes proceeds with a 'possible' or 'probable' working diagnosis of a brain AVM, as if the diagnosis was 'definite'. Further investigation may not be undertaken, and these people will be an interesting subgroup for future analysis. Subsequent events (such as ICrH or epilepsy) may lead to investigations that confirm the 'definite' existence of a brain AVM, which militates against the exclusion of these individuals.

Therefore, in any analysis, the level of certainty of the included patients' diagnoses will be specified.

3.2.3.5 Date of diagnosis

Some time after a patient presents, their IVM is diagnosed on the basis of radiological or pathological examination, according to the study's inclusion criteria (3.2.3, page 98). The earliest date of definite radiological/pathological diagnosis constitutes the 'date of diagnosis' of the IVM, when it is deemed to be 'incident' or 'detected'. Exceptionally, a person may harbour multiple definite IVMs, in which case each attracts a separate date of diagnosis [Chaloupka and Huddle 1998]. A patient's date of diagnosis, on the other hand, refers to the earliest date that any of their definite IVMs were diagnosed.

3.2.4 *Study setting*

3.2.4.1 Demographics of Scotland

The most recent decennial census in Scotland was conducted on 29th April 2001. At that time, the total population was 5,062,011 of whom 51.95% were female, 4,089,946 (80.8%) were aged ≥ 16 years, and 87% were born in Scotland. Scotland's population denominator is a manageable size for surveys of a condition like brain AVMs with an estimated incidence of 1-2 per 100,000 per year.

The size and age structure of the Scottish population at the time of this study were derived from annual between-census estimates. The General Register Office (GRO) produces these estimates using registration of births and deaths as well as data on

immigration and emigration (www.gro-scotland.gov.uk). The mid-2000 estimate of the population of Scotland was 5,114,600, of whom 4,114,052 were adults aged over 16 years. There was only a small (0.3%) annual flux in the population (immigration of 6,400 and emigration of 6,600 people) in the 12 months prior to 30 June 2000.

3.2.4.2 The Scottish health service

Few patients receive health care outside the National Health Service (NHS), almost every patient is registered with a general practitioner (GP), and there is negligible overseas and cross-border flow to England of the population for health care. The Information and Statistics Division (ISD) (www.show.scot.nhs.uk/isd) centrally registers and codes every death certificate and every hospital inpatient admission in the NHS in Scotland. There are four Neuroscience centres in separate health boards (Glasgow, Greater Glasgow; Edinburgh, Lothian; Dundee, Tayside; Aberdeen, Grampian) staffed by – amongst others – 32 consultant neurologists, 19 consultant neurosurgeons, and 71 consultant radiologists based at a Neuroscience centre or affiliated to another hospital providing CT, MR or IADSA. Patterns of investigation of ICrH probably vary depending on each clinical scenario and the facilities available. Compared to previous estimates, autopsy rates are declining [Cameron *et al.* 1977]; in the years 1999 and 2000 ISD data show that there were 118,080 adult deaths in Scotland, of whom 14,630 (12%) had a post mortem examination.

3.2.5 Ethical approval

At the time of this project, in Britain multicentre research was defined as taking place over five or more local research ethics committee (LREC) geographical boundaries, each LREC usually corresponding to a part or the whole of a healthboard. A multicentre application for ethical approval had to be submitted to a single multicentre research ethics committee (MREC) for an independent opinion on all the ethical and scientific aspects of the research proposal, and once approved, it had then to be distributed to every LREC in the geographical location of the study. Each LREC's executive subcommittee then judged the suitability of the local site, researcher(s) and facilities before the research could start in their area.

The MREC for Scotland (MREC/98/0/48) and every LREC in Scotland approved the following study methods, following a laborious application process, described in Chapter 16.

3.2.6 *Sources of case ascertainment*

SIVMS uses multiple overlapping sources of case ascertainment (Figure 10, page 116) to identify all adults meeting its inclusion criteria (see 3.2.1, page 97):

3.2.6.1 Collaborative neuroscience network

The primary source of ascertainment is an all-inclusive, collaborative network of clinicians, radiologists and pathologists working in the clinical neurosciences and stroke medicine (Chapter 19). Collaborators are not only based at the four neuroscience centres serving the population of Scotland, but also at the other hospitals in the country – and at neighbouring hospitals in the North of England – where brain imaging facilities are available. SIVMS steering committee members in Edinburgh and Glasgow also actively survey (and retrospectively check) the records of the two Scottish specialist brain AVM clinics for new cases. Although the vast majority of patients in Scotland receive healthcare through the state-funded NHS, I have ensured that the network also covers the few private facilities offering brain imaging and clinical consultations from relevant specialists. Collaborators receive monthly newsletters, reminders about the study by email, and use materials available on the study website (www.sivms.com) to notify the study of incident cases as they arise. Up-to-date information about any potential new collaborators in each hospital is obtained quarterly from the Steering Committee.

3.2.6.2 General practitioners

I estimated that each general practice in Scotland would have, on average, at least one adult with an IVM. I supposed that GPs would find these people memorable, so I contacted all 3,700 GPs in Scotland in January 2000, asking if any of their patients, who SIVMS did not already know about, were eligible for inclusion in the study. This

method of ascertainment was only used once, for the first year of the study, in view of its low yield (see 8.2, page 188).

3.2.6.3 Centralised coding of hospital discharge data and death certificates

In Scotland, every episode of hospital care is coded with details of a patient's main diagnosis, comorbidity (up to five subsidiary diagnoses), and any operations or procedures conducted. Diagnostic data from hospital discharges as well as death certificates are coded using the tenth revision of the International Classification of Diseases (ICD-10). In Scotland, all hospital inpatient stays (known as Scottish Morbidity Records, SMR01) have been collated since 1980, and are linked with death records from the GRO by ISD. Several mechanisms for ensuring data quality are in place at ISD, including validation, accreditation, quality assurance and monitoring, and national coding advice and training programmes [Harley and Jones 1996].

Every six months SIVMS requests records of adults (age ≥ 16 years) dying or discharged from hospital for the first time ever according to ISD's records with an ICD-10 code for a brain AVM in any diagnostic position (Table 11, page 115). The data upon which this thesis is based were provided by ISD in August 2001 for the complete years 1999 and 2000.

3.2.7 *Notification*

SIVMS receives notifications of potentially eligible patients on posted, faxed, or emailed notification forms from the collaborative neuroscience network or GPs (see appendix of study materials – 1 and 2), and from ISD in biennial delimited ASCII electronic files which are imported into the study database. SIVMS later thanks collaborators and GPs for their notifications, and informs them if the patients are excluded (see appendix of study materials – 3 to 8).

3.2.8 *Recruitment*

Following notification of a newly diagnosed patient from one of the sources of case ascertainment, SIVMS approaches a patient's GP and their main hospital consultant by post. An interval of four weeks is left to allow a discharge summary and/or brain imaging report to reach the clinicians before SIVMS approaches them. A structured letter seeks confirmation of the accuracy of the information supplied by the notifier, permission to access the patient's case notes, and questions about whether the patient is suitable for SIVMS to approach by post with a consent pack. These letters are customised according to whether the patient is alive, the patient's gender, whether the patient was identified by ISD, and whether the main consultant is a neurologist/neurosurgeon and whether they were responsible for notification (see appendix of study materials – 9 to 14 and 16 to 19). Whether SIVMS subsequently contacts the patient depends on how the GP and main hospital consultant respond. SIVMS approaches the consultant caring for the patient at any other hospital(s) the patient has attended four weeks after the main consultant's response and as and when other hospital attendances come to light (see appendix of study materials – 15).

Non-responders are pursued by a three-week reminder letter, and further pursued by letter or telephone if necessary.

Disagreements about whether a patient is aware of their diagnosis, caused by the lag in information passing from hospital consultant to GP, are resolved by correspondence. If access to case notes is denied on the grounds of cost by a GP, SIVMS negotiates reimbursement and/or agrees to go to the practice to copy the notes. If access to case notes is conditional upon patient consent and the patient has not been deemed to be aware of their diagnosis, SIVMS attempts to gain access to the notes by reassurance that explicit patient consent is not required for this by the MREC for Scotland.

Disagreements between GP and consultant about whether SIVMS should approach a patient with a postal consent pack are of most concern because SIVMS strives to obtain consent and questionnaire data from every living patient. SIVMS has little choice but to refrain from approaching a patient when a clinician's opinion is that they had been reassured about their prognosis and would be worried by an approach from a research study, or that the patient is too anxious or cognitively impaired for postal contact.

However, annual GP follow-up (see 3.2.10.1, page 108) is used as an opportunity to review the appropriateness of these decisions, should contact from SIVMS become appropriate at a later date (see appendix of study materials – 22).

For a patient to be approached with a consent pack, they must be alive, aware of their diagnosis and deemed appropriate for postal contact. Ethics committees regard a direct first communication from a research study to a patient to be unethical (so-called ‘cold calling’). For this reason SIVMS sends a patient consent pack to the patient’s GP, asking the GP to sign a pre-formatted letter introducing SIVMS and then to forward this letter with the consent pack in a pre-paid envelope addressed to the patient. The consent pack contains a letter from SIVMS to the patient, a consent form, an information leaflet about SIVMS, and a questionnaire requesting simple demographic details (see appendix of study materials – 21). On the consent form, patients are asked whether they permit access to their medical records and whether they are willing to complete annual questionnaires. If necessary, up to two reminders are sent to the GP at three-week intervals. If there is still no response from the patient after a further six weeks, attempts to gain their consent and completion of a questionnaire are abandoned until the annual follow-up procedure starts (see 3.2.10, page 108).

Following the conclusion of the recruitment process, each patient’s GP and main hospital consultant are sent a letter summarising whether SIVMS has access to notes and whether the patient has agreed to complete annual questionnaires (see appendix of study materials – 23 to 25).

3.2.9 *Collection of study materials during recruitment*

3.2.9.1 Medical records

SIVMS allows at least 8 weeks to pass following a patient’s diagnosis before requesting copies of medical records from every hospital where they have been seen as an inpatient or outpatient and from their GP (see appendix of study materials – 26 to 29). An interval of at least 3 weeks following a patient’s death is left before requesting the GP

case notes to allow for their passage to one of the three Practitioner Services² regional medical offices where they are usually kept for 3 years and then destroyed.

Deferring these requests is intended to allow completion of secretarial and administrative tasks relating to the patient's diagnosis/death. Additional delays may be incurred if clinicians do not return the recruitment forms, or if there is a dispute about patient consent, cost or access to case notes. SIVMS requests notes from the neuroscience centre as well as any referring hospital(s) to ensure that information is obtained about the mode of a patient's presentation, which may well have occurred elsewhere.

A reminder is sent if case notes have not been received within 3 weeks, and non-responders are contacted by telephone.

3.2.9.2 Diagnostic brain imaging

At least four weeks after diagnosis, SIVMS enquires about the extent of brain imaging at the hospital where the diagnosis was made (and the referring hospital, if appropriate). The relevant CT, MRI and IADSA studies are requested by telephone, and if they are not received within 3 weeks, non-responders are contacted by telephone. Once received, I review the brain imaging. Apart from the IADSA sequences that demonstrate vascular territories not involving the brain AVM, hard copies of each complete imaging study are made and transported to the image library filing cabinet at the Institute of Neurological Sciences in Glasgow to await review by the study neuroradiologists at their consensus meetings.

3.2.9.3 Patient questionnaire

If SIVMS is permitted to approach a patient by their GP and main hospital consultant, the postal consent pack contains a questionnaire that cross checks demographic details

² These Practitioner Services teams are divisions of the Common Services Agency, NHSScotland, and register patients with family doctors on the population database (the Community Health Index – CHI), maintain the integrity of the index, transfer the medical records of these registered patients, and process payments to GPs

including ethnicity, and enquires about handedness, number of children, medical history, current medications, and family history (see appendix of study materials – 21).

3.2.10 *Collection of study materials during follow-up*

Patients are followed-up on an annual basis during their lifetime using several overlapping methods.

3.2.10.1 GP questionnaire

Every patient's GP is contacted six weeks before the anniversary of the patient's diagnosis (see appendix of study materials – 30 and 31). A single-page GP questionnaire seeks confirmation of the patient's address and enquires about whether they are still suitable for postal contact, or whether it is now appropriate to send a postal consent pack if it had not been before. The questionnaire also validates survival and asks about hospital visits/admissions in the preceding year, the occurrence of brain haemorrhage and epilepsy, and asks the GP to assess the patient's current disability on the Rankin scale [Rankin 1957]. A reminder letter is sent after 3 weeks, and GPs are telephoned after a further 3 weeks if they still do not reply.

3.2.10.2 Patient questionnaire

Participants are contacted directly if they have already consented to complete annual questionnaires and if their GP – in their annual questionnaire (above) – has confirmed that the patient is both alive and still suitable for a questionnaire. For example, it might be inappropriate to send a questionnaire in the event of a recent ICrH resulting in hospitalisation.

The patient questionnaire includes postal versions of the Barthel Index, Short-Form 36, and Hospital Anxiety & Depression Scale [Mahoney and Barthel 1965; Zigmond and Snaith 1983; Ware 1993], questions about epistaxis and telangiectasia (screening for HHT), and two questions screening for the occurrence of headaches and epilepsy (see appendix of study materials – 34-36). If a participant claims to be, 'significantly bothered by recurrent headaches' they are sent a further questionnaire screening for migraine

[Tom *et al.* 1994]. If they claim to have, 'epilepsy (seizures or fits)' then they are sent a further questionnaire attempting to define seizure type (which although not validated, has been used in a community postal survey by the Walton Centre, Liverpool [Jacoby *et al.* 1996]).

If the patient does not respond to the main questionnaire, postal reminders are sent after 3 weeks and if necessary after a further 3 weeks, but attempts are abandoned if a reply has still not been received 3 months after the second reminder. Patients are reminded about returning their headache and epilepsy supplementary questionnaires once only, 3 weeks after they were first sent.

3.2.10.3 Medical records

Each year SIVMS requests copies of case notes held by the GP and every hospital the patient has visited (see appendix of study materials – 32 and 33). In order to minimise contact with GPs, SIVMS makes this request at the same time as the annual GP questionnaire is sent (see 3.2.10.1, page 108). Hospital case notes are requested one year after the last request was made, provided the patient has not been discharged from the consultant's care. The letters sent merely request correspondence *subsequent* to the date of the most recent letter in the SIVMS notes obtained from the GP/hospital records. Postal reminders are sent after 3 weeks.

3.2.11 Collection of materials when a patient dies

Whether a patient has died during recruitment or follow-up, SIVMS still obtains the entire set of GP case notes from Practitioner Services (to ensure that all potentially relevant correspondence has been copied), copies of hospital case notes, and copies of diagnostic brain imaging (if the IVM was diagnosed during life). An electronic copy of the patient's death certificate is obtained from the GRO, and autopsy and neuropathology reports are requested if a post mortem was performed.

3.3 Study audit

There are various measures taken to prevent poor data quality, detect imperfect data and their causes, and institute necessary corrective action during case ascertainment, recruitment, collection of medical records and brain imaging, and patient consent. As data are entered, reminders appear to prevent duplicating a patient's inclusion in the study and there are basic compulsory data entry requirements to ensure the collection of a minimum dataset. The study database runs several routine procedures invisible to the user (using 'queries' – see Chapter 4), to ensure data are appropriately updated and cross checked and events (such as triggering annual questionnaires) are initiated at the appropriate time. Occasionally, exceptions to the usual process of the study mean that further safeguards are required to maintain data quality and accuracy. For example, ascertainment of a patient three years after their first diagnosis might normally result in three annual questionnaires being sent because the process is triggered by the time interval that elapses since diagnosis, were it not for compensatory processes to modify the data when this occurs.

Progress is reviewed at weekly meetings with my supervisor. This provides an opportunity to check the effectiveness of SIVMS's procedures and troubleshoot individual doctors' or patients' objections to the study. Year-on-year recruitment, quality and completeness of data, and interim analyses are presented at biennial steering committee meetings. Reports are produced on the basis of these data at the request of SIVMS's sponsors. These data will be presented in a later chapter on data quality (Chapter 7).

3.4 Summary

- SIVMS aspires to meet the standards of an ideal study of prognosis, as defined in Chapter 2 (Table 4, page 85)
- SIVMS includes adults who were aged ≥ 16 years at the time of a first-in-a-lifetime diagnosis of an IVM made ≥ 1 January 1999, when they were resident in Scotland

- This thesis, however, only pertains to the adults with brain AVMs, diagnosed between 1 January 1999 and 31 December 2000
- The SIVMS neuroradiologists divide brain AVM diagnoses into definite, probable and possible on the basis of diagnostic criteria
- Whilst the point of inception is the presentation that led to the brain AVM diagnosis being made, the incidence date is the year in which the definite diagnosis was first made
- Cases are recruited using multiple overlapping sources of case ascertainment (a collaborative neuroscience network, central coding of hospital discharge data and death certificates, and a mailshot to every GP in Scotland, used in the first year of SIVMS only)
- Recruitment and data collection are controlled by a Microsoft Access database, with in-built audit processes

3.5 Discussion

In this chapter, I have provided a description of the stages of the study through which a patient may (or may not) pass. As SIVMS evolved, complexity increased because of unforeseen problems, which sometimes resulted in a modification of the study's methods. This description is correct at the time of writing (2002-2003).

3.5.1 *Inclusion*

I have tried to retain inclusion and exclusion criteria that are robust and externally valid. Because of its population-based design, SIVMS has tended to be over-inclusive, with a brain AVM working definition that does not rely on IADSA, which is likely to be available only at tertiary referral centres. A definition reliant on IADSA would miss diagnoses made on CT, MRI or pathological examination alone, and ignores the existence of AOVMs [Joint Writing Group 2001]. Although such a definition might foster complete collection of variations of vascular anatomy (angioarchitecture) that are of interest as prognostic factors, it would be likely to bias studies towards patients having extensive investigation, under-estimate the true frequency of brain AVMs, and

under-estimate their importance as a cause of sudden death by missing post mortem diagnoses. Furthermore, the flexibility of including anyone with a definite, probable or possible brain AVM, enables the prospective follow-up of uncertain diagnoses that may subsequently change, the description of the clinical course of such lesions, and a *post hoc* ability to stratify analysis by certainty of diagnosis (and/or its verification by IADSA).

3.5.2 *Recruitment*

The sources of case ascertainment used by SIVMS were based upon the successful collaboration used by the Scottish Motor Neurone Disease Register [Chancellor *et al.* 1993], albeit with the addition of other relevant specialities (e.g. neurosurgery and radiology). I considered other potential sources of case ascertainment, but none was suitable at the time of setting up the study, although this may change. The British Neurological Surveillance Unit (BNSU) is run by the Association of British Neurologists (ABN) and functions as a postal means of detection of specified neurological diseases. I found it unnecessary to use the BNSU because I already contacted every neurologist in Scotland (and they are not all members of the ABN), so the use of the BNSU would entail needless cost and use of a 'middleman'. A more attractive source of case ascertainment would have been an electronic search of free text and/or diagnostic coding amongst radiology reporting systems across Scotland. I surveyed all the radiology departments with CT, MRI and IADSA facilities across Scotland at the start of SIVMS, and found that the technological limitations of the reporting systems in use at the time made electronic searching for diagnoses impossible.

The timing of SIVMS's recruitment efforts was derived from the anticipated duration of standard processes in the NHS, such as relaying diagnostic information from secondary care to GPs. In the first year of SIVMS, the timing of study letters and reminders was refined to allow more time for information to filter to GPs and consultants, given the unpredictable variation in process I observed in the NHS. The recruitment process, with its in-built pauses, would take several months, let alone the delays incurred by non-respondents, disagreements between GP/consultant, objections to the study, and time to obtain (and review) diagnostic brain imaging.

3.5.3 *Technological enhancements*

I considered other means of using technology to the study's advantage, apart from electronic searching of radiology reporting systems. Early on, case ascertainment and notification by post/fax/telephone seemed convenient and time-effective for SIVMS collaborators, without the need for web-based data collection systems. Concerns about the safety of data transmission via the Internet as well as the ease of use and efficacy of digital encryption technologies meant that some of our collaborators would have been unhappy to employ this, which precluded its further development. Digitising brain imaging would provide an invaluable electronic archive, thereby protecting vital study data (sometimes not permanently archived by radiology departments on optical disc) and potentially making it available for studies of observer variability and multimedia teaching tools. Sadly, this has not met with unanimous approval from the steering committee.

3.5.4 *Comparison with other studies*

SIVMS surpasses the existing literature about IVM frequency and prognosis (Chapter 2), by providing clear diagnostic definitions, aiming to attain comprehensive and representative recruitment from a whole population using multiple overlapping sources of case ascertainment, and specifying a uniform inception point from which patients are prospectively followed. The mechanism of follow-up is designed to make an annual record of a patient's survival at the very least, and for the vast majority a record of major outcomes (death, haemorrhage, epilepsy and disability on the Rankin scale) by several means. Although the chosen measures of functional status have not been validated in groups of people with IVMs, they have been well used in adults with stroke and epilepsy.

The variable and sometimes complex processes that lead to recruitment and data collection at baseline and during follow-up are all managed by a database, the architecture of which I will describe in the next chapter.

Table 10 Broad definitions of the different levels of radiological certainty of brain AVM diagnosis

CT = computed tomography; MRI = magnetic resonance imaging; IADSA = intra-arterial digital subtraction angiography

Certainty	CT	MRI	IADSA	Pathology
Definite	Anastomosis of non-nutritive blood vessels in the brain parenchyma, with an apparent nidus. The vessels enhance with the administration of intravenous contrast.	Anastomosis of non-nutritive blood vessels in the brain parenchyma, with an apparent nidus. Serpiginous cluster of flow voids on standard spin-echo MRI (T ₁ and T ₂).	Anastomosis of non-nutritive blood vessels in the brain parenchyma, with arteriovenous shunting in a nidus. Early visualisation of draining veins during the late arterial or capillary phase on rapid sequence angiography.	Anastomosis of non-nutritive blood vessels in the brain parenchyma, with arteriovenous shunting in a nidus. The vessels have a mature phenotype, morphologically between arteries and veins, and intervening capillaries are missing.
Probable	Anastomosis of non-nutritive blood vessels in the brain parenchyma, with an apparent nidus and possibly vessel calcification. Intravenous contrast not given.	Anastomosis of non-nutritive blood vessels in the brain parenchyma, with an apparent nidus. Flow voids suggestive of feeding arteries and draining veins, but no clear nidus.	Anastomosis of non-nutritive blood vessels in the brain parenchyma suggested by early visualisation of a draining vein during the late arterial or capillary phase on rapid sequence angiography. No nidus or direct arteriovenous fistula visible.	Not used
Possible	Apparent vascular mass in the brain parenchyma, which may be accompanied by vessel calcification and/or parenchymal calcification (from presumed prior haemorrhage). Intravenous contrast not given.	Apparent vascular mass in the brain parenchyma, with no clear flow voids suggestive of feeding arteries or draining veins.	Early visualisation of a vein during the late arterial or capillary phase on rapid sequence angiography, but no nidus, dilated feeding arteries or direct arteriovenous fistula visible.	Not used

Table 11 Diagnostic codes pertinent to brain AVMs in the tenth revision of the International Classification of Diseases (ICD-10)

D In situ neoplasms

D18 Haemangioma and lymphangioma, any site

D18.0 Haemangioma, any site

I Diseases of the circulatory system

I60 Subarachnoid haemorrhage

I60.8 Other subarachnoid haemorrhage

I60.80 Rupture of specified arteriovenous malformation

I67 Other cerebrovascular diseases

I67.1 Cerebral aneurysm, nonruptured (including acquired cerebral arteriovenous fistula)

I77 Other disorders of arteries and arterioles

I77.0 Acquired arteriovenous fistula (aneurysmal varix, acquired arteriovenous aneurysm; excluding cerebral (I67.1))

Q Congenital malformations, deformations and chromosomal abnormalities

Q27 Other congenital malformations of peripheral vascular system

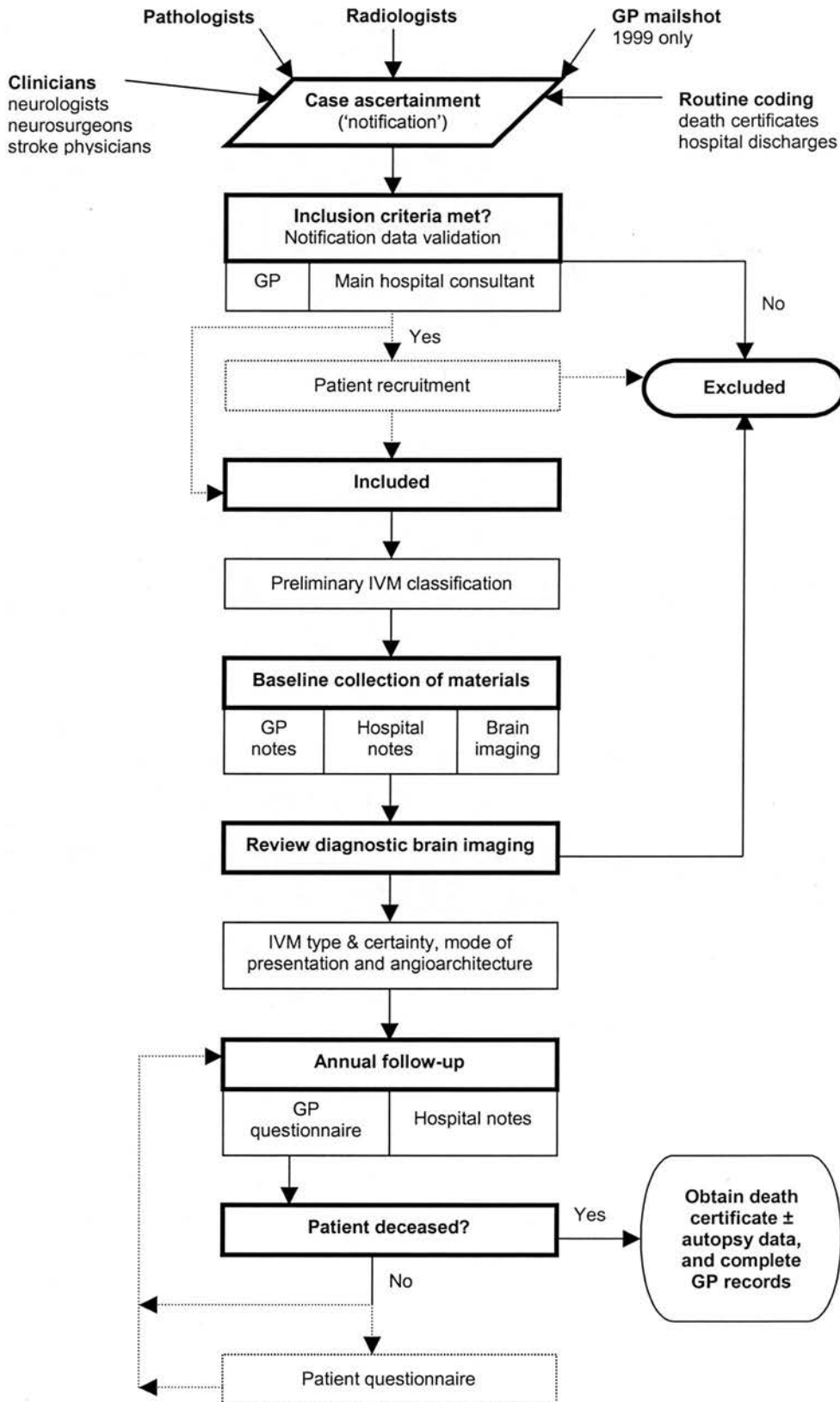
Q27.3 Peripheral arteriovenous malformation

Q28 Other congenital malformations of the circulatory system

Q28.2 Arteriovenous malformation of cerebral vessels

Q28.3 Other malformations of cerebral vessels

Figure 10 Scottish Intracranial Vascular Malformation Study flowchart
Dashes indicate events dependent on patient participation/suitability



Chapter 4. Database design for a population-based disease register for adults with intracranial vascular malformations

Chapter contents

- 4.1 Introduction
- 4.2 Design
 - 4.2.1 Relational databases
 - 4.2.2 Added advantages of Access
- 4.3 Data protection and confidentiality
- 4.4 Data security
- 4.5 Backup
- 4.6 Summary
- 4.7 Discussion

4.1 Introduction

The subject matter and methods of this research project present various degrees of complexity and unpredictability; these are ideally managed by a database, yet present challenges for its design.

For example, although IVMs usually exist as solitary lesions in patients' brains they may be multiple, they may be diagnosed with certainty at different times, and some may develop *de novo* over time. Furthermore, IVM structure ranges from the simplicity of a single transcortical venous malformation to a large, complex brain AVM with various numbers of draining vein(s), arterial feeder(s) and associated aneurysm(s). Although each patient's ideal flow through the study is clearly defined (Figure 10, page 116), there is considerable heterogeneity in their clinical state and subsequent clinical course, as well as heterogeneity in their own preferences and those of their GP and hospital consultant(s).

A manual paper-based system might have sufficed with careful management by the SIVMS secretary and myself. However, the availability and the capability of database software compelled me to use Microsoft Access 97 (hereafter referred to as Access) to manage study recruitment, follow-up and data collection.

4.2 Design

Before embarking upon the study, I modelled the data I intended to collect and the processes I would use to manipulate it. These models were then mapped to the ideal 'relational' database structure offered by Access. This data-centred discipline undoubtedly avoided several preventable errors, although subsequent restructuring and reorganisation of the data were inevitable.

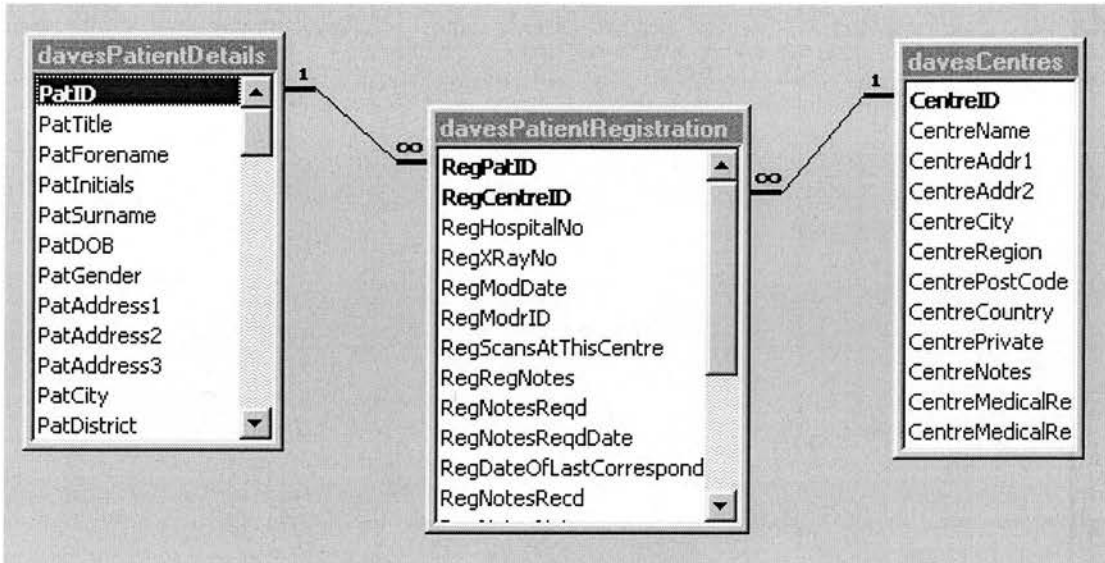
On the grounds of flexibility, I had been encouraged to adopt a database design that corresponded to the *natural structure* of the information I wished to store. If I had not done this, over-simplification of data could have led to inflexible analysis, preventing the exploration of real-world association/causation. However, I later came to appreciate how reflecting the complexity of the natural structure of IVM and patient data would make data analysis more versatile but the programming more difficult.

Although the database is the principal means of managing patients' progress through SIVMS and analysing data, the most comprehensive dataset is stored on paper in individual sets of case notes bearing each patient's study number. Copies are kept of the notification form(s), as well as all correspondence about study enrolment with patients and their GPs and hospital consultants, complete copies of case notes, and GP and patient follow-up questionnaires. However, a large number of these data are abstracted by the relevant member of the study team and manually entered in the database to enable automated processing of patients through the study and systematised data analysis. The paper record remains a source of reference for future clarification, or exploration of other hypotheses using information not specified in this thesis.

4.2.1 *Relational databases*

Access is a relational database. Such databases store sets of data in 'tables' (composed of columns and rows). These data are related to each other, and the related tables are linked using variables ('fields') common to both tables. The designer can specify the types of relationships between separate tables of information.

For example, one patient may be cared for at several hospitals, in which case the relationship between the patient and hospital tables is described as 'one-to-many'. This enables the details at each separate hospital to be linked to the same patient, simply using the patient's study number in the hospital table. In the diagram overleaf, the patient table ('davesPatientDetails') is linked to the hospital table ('davesPatientRegistration') by a one-to-many relationship between the common fields containing each patient's study number. This is represented by a line with a figure 1 and an infinity symbol at each end, indicating the direction of the relationship. There is a similar relationship between the hospital table ('davesPatientRegistration') and a 'look-up table' containing the address of each hospital ('davesCentres').



The other types of relationship are one-to-one and many-to-many. The latter is usually best decomposed by using an intermediate 'junction table' with a one-to-many relationship to each of the tables it links (as above).

Relational databases have many strengths. Subdivision of data into separate tables of variables avoids unnecessary repetition of data (for example, every time a hospital is referred to, only its code number in the look-up table above is used). Several small tables are easier to manage (and subsequently modify) than one large table of variables. A relational database can also reflect the natural structure of the information being stored (for example, each patient usually harbours one IVM, but may harbour many IVMs, best reflected by a one-to-many relationship between the patient and IVM tables).

4.2.2 *Added advantages of Access*

Access is a fully featured 'rapid application development' environment for creating database applications on both single-user and networked personal computers. Access offers more than just a flexible means of storing data in tables. 'Queries' extract, manipulate and summarise data stored in tables. Access executes these queries using structured query language (SQL), and its distinct advantage is its graphical query development tool that requires no knowledge of SQL from the user. The data – held by tables and derived using queries – are visually presented on the computer screen using

custom-designed 'forms', and are printed as customised 'reports'. Complex procedures involved in query design, navigation between forms, and executing automated procedures (such as running audit and reminder queries when a particular user opens the database) are handled by user-defined 'macros' and programming in Visual Basic and SQL statements. These are beyond the scope of this thesis.

Access has the added advantage of being able to both link to and/or import other collections of data, via Open Database Connectivity (ODBC) drivers. For example, routine hospital discharge and death certificate data supplied by ISD in dBase and Microsoft Excel are imported into Access in a standardised format so that they may be appended to core tables, and further processed according to SIVMS's standard procedures. The SIVMS database also links to other collections of data on the DCN network which – although static in their structure and location – are regularly updated (for example, databases of Scottish GPs and their practices).

Furthermore, Access interacts with Microsoft Word by using the Mail Merge function in Word. Standardised letters (see appendix of study materials) are reproduced only for patients meeting certain criteria, specified in queries in Access. By running these queries every time the SIVMS secretary opens the database, Mail Merged letters and reminder reports ensure that patients' progress in the study is regularly addressed.

The SIVMS database is divided into two separate components. The data file ('SIVMS-data.mdb') contains the tables of data, and the application file ('SIVMS.mdb') contains the queries, forms, reports, macros and 'modules' (the latter collate various procedures). The tables are linked to the application file. One advantage of this structure is that the application file can be updated without disrupting the data file, and vice-versa. In SIVMS's multi-user environment, the data file is shared on a networked server, which enables all its users to update the same copy of the database simultaneously. The application component is also networked, but once its development is complete each user will ultimately have their own copy of the application file (which will reduce network traffic, and so speed up database use).

4.3 Data protection and confidentiality

Of central importance to medical research is the protection of data by restricting access to them, and the maintenance of patients' confidentiality by the removal of associated information that could identify them. These are related: confidentiality is enhanced by data protection when information that identifies a patient is used.

Several conflicting pressures face medical researchers when deciding whether and how to use identifiable data about patients; these are discussed in Chapter 17. Because of the design of SIVMS – which relies upon other agencies to provide copies of medical records, brain imaging, and follow-up information – referring to patients by name and using other identifiable information about them is an absolute necessity. SIVMS's use of such data is sanctioned by the MREC for Scotland, and covered by the University of Edinburgh's registration with the Data Protection Act (1998).

The data held by SIVMS which are deemed – either alone or in combination – to be patient-identifiable information are: name, date of birth, Community Health Index (CHI) number (a composite of date of birth and another number), address, telephone number, email address, next of kin details, and hospital identification numbers (for case notes, imaging, and pathological examinations).

Were it not essential to identify patients, various strategies are available to protect access to patient-identifiable data. Ultimate protection is offered by *irreversible anonymisation*, in which data are stripped of identifiable details either at source or after receipt, with no means of re-establishing a patient's identity. Data may be *reversibly anonymised* (*pseudo-anonymised* or *pseudonymised*) by de-identifying them and attaching a unique code (which is mapped to each patient's details in a separate file).

SIVMS employs pseudonymisation when exporting data for reference or analysis (whether this is done in-house or by collaborators at another institution), using patient study number as the only identifier. Confidentiality of stored data is not safeguarded in this way, because of the need for identifiable information, but rather it is protected by elaborate security.

4.4 Data security

Within the University of Edinburgh's local area network (LAN) the DCN has its own dedicated servers, which are physically located in the DCN and are protected from external threats by a firewall. One of these servers (DCN-skull) contains a networked drive (G drive), within which there are a variety of directories and subdirectories. The SIVMS database resides in the 'SIVMS' subdirectory of the 'Data' directory of the G drive (G/Data/SIVMS/).

Not only does access to the DCN's network require an individual username and password, but the network administrator restricts access privileges to G/Data/SIVMS/ to members of the study team currently working on SIVMS. Furthermore, to be able to open the Access database, users require another username and case-sensitive password, co-ordinated by an Access electronic workgroup file (which is encrypted). The permission assignments granted to each user are also managed by this workgroup, preventing some users from modifying design and data by granting them read-only access rights. Accountability is achieved by automatically updating each entry in each table with the identity of the user who last modified it. One further case-sensitive password is required to open the separate data file of the database allowing modification of the data architecture. Overall, between three and four layers of security protect SIVMS data.

4.5 Backup

The contents of the Data/SIVMS subdirectory of the networked G drive are backed up onto tape on a daily basis. These tapes are held centrally by the University of Edinburgh, and files (such as the SIVMS database) can be restored from a particular time and date. Another mechanism of data recovery is from Access backup files if users create them as they exit the database. The data, application and security workgroup information files of the database are backed up onto a disc on a weekly basis and stored off site in a fireproof locked safe.

4.6 Summary

- SIVMS stores paper records of study materials and identifiable data collected for every individual in the study, the fundamentals of which are stored in an electronic relational database
- A customised database application has been created using Microsoft Access, which effectively runs the study, imports data (e.g. information from secondary data sources) and exports data (e.g. for Mail Merge using Microsoft Word)
- The database is password-protected, resides on a secure network, allows multiple users to update it simultaneously, and it is regularly backed up

4.7 Discussion

Seldom does database design warrant a chapter of a thesis, but it is in this case because of the extent of data modelling and development of automated processes for managing recruitment and follow-up. The database has become more than simply a vehicle for data storage and subsequent extraction (this being all that is required of most observational datasets), but more like a randomised trial's software which checks and acts upon the data according to certain criteria – in essence, it is a customised application.

The design of the database evolved alongside modifications to study methods. For example, in the first year of the study, having gained the unanimous approval of both GP and main hospital consultant to approach a potential recruit, SIVMS would mail the patient a recruitment pack directly. But the MREC later revised their opinion, because this method involved 'cold calling' the patient (i.e. the approach to join the study came from an organisation potentially alien to them). Instead SIVMS now has to ask the GP to sign a covering letter and forward it with the recruitment pack to the patient. Such an apparently simple modification required the creation of new fields in the database, transposition of existing data about when recruitment letters were last sent, re-design of queries, the formation of new mail merges with the new GP letters, and reconfiguration of reminder forms and reports for the SIVMS secretary.

So far, data have been exported from the SIVMS database on only one occasion. The radiological data collected by reviewing diagnostic brain imaging have been exported to a separate database for the use of the custodian of the SIVMS imaging library in Glasgow (Dr Jo J Bhattacharya). The data were reversibly anonymised (i.e. patient study numbers were the only identifiers), but the data were not encrypted. The database was transferred in person, but if it had been posted I would have used registered/recorded delivery.

Password protection and restricted network access are the mainstay of SIVMS database security. The study does not routinely use encryption, except for encouraging its use in emailed patient notifications. Nor does SIVMS encourage regular changes of password, and a SIVMS security clause has not been added to staff contracts. These are all potential future security developments.

Based on the premise that high quality clinical databases will benefit from sharing knowledge and data, and that centralising them will promote this aim [Black 1999], SIVMS has become part of the UK Directory of Clinical Databases (DocDat) (www.lshtm.ac.uk/docdat/). Apart from simply indexing databases, DocDat also lists the data they collect and judges them according to the quality of their data, all of which I address in the next three chapters.

Chapter 5. Variables relating to patients with brain arteriovenous malformations and their clinical features

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5.1 Introduction

The foregoing chapters about the methods of SIVMS and the principles of its database design apply equally to all IVMs. However, the morphological and clinical differences between the various IVM subtypes require that this and subsequent chapters refer only to the main focus of this thesis, brain AVMS.

This chapter defines the demographic and clinical data that are stored about each patient with a brain AVM. Whilst some of these data are routinely collected and factual, others rely on medical concepts that may be perceived differently by different doctors (for example, what type of epilepsy a patient has). Systematically reviewing the brain AVM literature (Chapter 2) has revealed how few studies used clearly defined variables. To give SIVMS internal validity by standardising the assessment of each patient, I intended to clearly define the variables that would be collected before the study started.

A challenge to maintain external validity emerged in the third year of SIVMS with the publication of reporting terminology for brain AVM radiographic and clinical features by a multidisciplinary North American Joint Writing Group [Joint Writing Group 2001], and latterly with the publication of the design of a similar study to SIVMS, the New York Islands AVM Study (NYIAVMS) [Stapf *et al.* 2003]. I have highlighted any areas where SIVMS differs, but fortunately similarities in definitions have meant that there has been little need for modification, so internal validity has not been jeopardised.

5.2 Types of variable

The majority of variables in SIVMS are either known entities (for example, dates of responses to patient or GP questionnaires) or radiological/clinical concepts (for example, the nature of a patient's epilepsy, or variants of angioarchitecture). Fewer variables are derived (for example, a patient's duration of follow-up is determined by the comparison of several dates).

Wherever possible, variable contents are one of a limited list of categories, a number or a date, rather than being free text character strings (which are much more difficult to summarise and analyse). Date entries are stored in a standard format (dd/mm/yyyy); the 15th of the month is used for an event when its exact day is not known but the month

and the year are, and the 1st July is used when the day and month are not known but the year is. Variables with yes/no properties avoid check boxes and tend to use drop-down lists with the options 'yes', 'no' and 'unknown'; otherwise a blank field would be ambiguous, potentially indicating that the data were either not collected or were unknown.

5.3 Demographic variables

Basic demographic variables (such as name, sex and date of birth) are initially derived from study notifications. The research fellow (myself 1999-2001) subsequently cross-checks them against clinical records when they become available, although the ultimate arbiter of their accuracy is the patient themselves if they are approached with an enrolment form.

Ethnicity is solely determined by the patient, and uses the Office of Population Censuses and Surveys (OPCS) criteria because of their widespread use (White, Black-Caribbean, Black-African, Black-other, Indian, Pakistani, Bangladeshi, Chinese, Other, Unknown). Handedness is categorised as right, left, ambidextrous or unknown. Marital status is categorised as single, married, divorced, widowed, cohabiting, or estranged. CHI numbers are obtained either when making enquiries about a patient with the Health Board, or in periodic batches from ISD.

5.4 Clinical features

SIVMS records all clinical events that affect patients, whether before, at, or after the time of presentation (5.4.3.1, page 135). The concept of a 'clinical event' can only be loosely defined, but is best regarded as new symptom(s) (with or without signs) that represent a significant change from the patient's clinical state immediately preceding the 'event'. These data are derived from case note review, GP annual questionnaires, and patient annual questionnaires; the source of the information is specified for every event.

Clinical events possibly related to a patient's brain AVM(s)/aneurysm(s) are recorded as being of a particular type and occurring on a particular date. Each event is attributed to

both the patient in question and to the relevant brain AVM/aneurysm (with an indication of how certain I was that the brain AVM/aneurysm was the cause).

Clinical events that are completely unrelated to a brain AVM or aneurysm are stored separately. A patient's other/past medical history is subdivided into neurological and systemic comorbidities, and stored in two free text fields in the database. Patient enrolment forms and/or review of case notes provide information about a potential family history of brain AVMs, and its nature. An attempt is made to record the drugs a patient is taking and their start and end dates, although this information is likely to be moderately accurate, at best. A rudimentary obstetric history is also stored, with start and end dates for each pregnancy abstracted from case notes, and the number of children at the time of recruitment is requested on the patient's enrolment form.

The remainder of this chapter is an attempt to define different types of clinical events, to decide what caused them, and to be clear about their timing.

5.4.1 *Types of clinical events*

Depending on the individual case, brain AVMs can usually be confidently said to cause ICrH and epilepsy. They are probably the cause of FNDs referable to the anatomic location of the AVM nidus (in the absence of haemorrhage or infarction, usually on brain imaging), and are likely to cause subjective vascular bruits. But brain AVMs' role in causing headache, brain infarction and cognitive impairment is less clear.

5.4.1.1 Intracranial haemorrhage

A clinical event is classified as a haemorrhage if there are clinical features of ICrH with radiological, pathological, surgical, or – rarely – only cerebrospinal fluid (CSF) evidence of recent haemorrhage. The clinical features of haemorrhage may be sudden/subacute onset headache \pm seizures \pm global neurological deficit \pm focal neurological deficit referable to the anatomic location of the brain AVM nidus. Radiological evidence of acute haemorrhage is defined as fresh blood of high density on CT, or high density methaemoglobin on T₁-weighted MRI (6.5.1, page 156). If the haemorrhage is classified as 'radiographically proven', the imaging study number is also stored. Very occasionally,

there is no supplementary evidence to support a strong clinical suspicion of haemorrhage, and these haemorrhages are classified as 'clinically probable'. Only the following types of haemorrhage are specified:

Subtypes of intracranial haemorrhage

Intraparenchymal

Intraventricular

Subarachnoid

Intraparenchymal & subarachnoid

Intraventricular & subarachnoid

Intraparenchymal & intraventricular

Intraparenchymal, intraventricular & subarachnoid

Subdural

Unknown

This classification of haemorrhage complements the definitions used by the NYIAVMS and Joint Writing Group.

5.4.1.2 Epilepsy

Any occurrence of an epileptic seizure is classified according to the 1989 International League Against Epilepsy (ILAE) classification [Commission on Classification and Terminology of the International League Against Epilepsy 1989]. The recent update of the ILAE classification post-dates the set-up of this study. Seizure type is categorised as one of the categories overleaf, within the limits of the data available in the patient's case notes or from a patient's annual postal epilepsy questionnaire.

Subtypes of epilepsy

Simple partial \pm secondary generalisation

Complex partial \pm secondary generalisation

Generalised

Status epilepticus

Unknown

At each mention of epilepsy in case notes or questionnaires the following additional data are stored, where available: epilepsy activity [inactive (<1 /year), active (<1 /month), active (>1 /month), unknown], whether the patient is treated (on anti-epileptic drugs, off anti-epileptic drugs, unknown), and the timing of the seizures (day, night, either, unknown).

5.4.1.3 Focal neurological deficit

FNDs are clinical impairments referable to the anatomical location of the brain AVM nidus, that are neither migrainous, nor post-ictal, nor found to be due to haemorrhage or infarction after radiological investigation [Mast *et al.* 1995]. They are further classified as transient (lasting <24 hours), persistent (lasting >24 hours), or progressive (lasting >24 hours with further deterioration). Figure 11 (page 140) illustrates the decision-making process in categorising focal neurological symptoms \pm signs.

Considerable controversy surrounds the pathophysiology of these FNDs. Some argue that vascular 'steal' explains them, while others disagree and feel it is venous hypertension. Distinguishing this type of event from a clinically probable haemorrhage (for which no radiological investigation was performed) may be difficult; because it is a matter of subjective judgement it would need to be independently evaluated by another SIVMS investigator. It is possible that transient deficits might be due to feeding arterial stenosis or transient ischaemic attacks, and that persistent deficits might be due to haemorrhage/infarction that was not investigated at the right time or with the appropriate type of imaging, or was too small to be seen on CT/MRI.

5.4.1.4 Headache

Determination of headache type is attempted from case note review and patient postal questionnaires, according to the first International Headache Society (IHS) classification [Headache Classification Committee of the International Headache Society 1988]. The recent second IHS classification post-dates the set-up of this study.

Subtypes of headache

Associated with head trauma

Associated with metabolic disorder

Associated with non-cephalic infection

Associated with non-vascular intracranial disorders

Associated with substances or their withdrawal

Associated with vascular disorders

Cluster and chronic paroxysmal hemicrania

Cranial neuralgias

Nerve trunk pain and deafferentation pain

Headache or facial pain associated with facial or cranial structures

Migraine

Miscellaneous

Unassociated with structural lesion

Tension type

Not classifiable

Unknown

At each mention of headache in case notes or questionnaires, an estimate of its frequency is made: none, < 1 / month, > 1 / month, unknown.

5.4.1.5 Incidental

This category is only used for *presentations* (5.4.3.1, page 135), when the investigation(s) that led to the brain AVM diagnosis being made were prompted by symptoms/signs that may possibly – but not definitely – be due to the brain AVM or symptoms/signs attributable to something else. For example, headache, brain infarction and cognitive impairment might only possibly be due to a brain AVM; asymmetrical sensorineural hearing loss, chronic sinusitis, and head trauma might also lead to brain imaging and incidental detection of a truly ‘asymptomatic’ brain AVM. Long before diagnosis, these patients may have experienced symptoms that were likely to have been – in retrospect – due to the brain AVM (see 5.4.3.2, page 136), but their *presentation* is nevertheless ‘incidental’.

5.4.1.6 Infarction

Infarctions are classified according to the Oxfordshire Community Stroke Project (OCSP) classification as involving the total/partial anterior circulation, lacunar or posterior circulation [Bamford *et al.* 1991]. These events are classified as being supported by radiological and/or pathological evidence, or the diagnosis may be made on clinical acumen only.

5.4.1.7 Cognitive impairment

Cognitive impairment is recorded without a degree of severity, and is simply recorded to give an idea of its burden on patients with brain AVMs, rather than as a meaningful outcome that can be quantified by SIVMS’s methods of follow-up.

5.4.1.8 Other

This category encompasses a variety of symptoms and signs that may be attributable to a brain AVM but have no category of their own (e.g. an abnormally dilated vein on the forehead leading to the diagnosis of a brain AVM with external carotid artery supply). For patients with incidental presentations of truly asymptomatic brain AVMs, a clinical

event 'other' is entered coinciding with the date of presentation, to provide further information about what led to AVM detection.

5.4.1.9 Tinnitus/bruit

This is a category that subsumes the variety of patients' subjective experiences of noises heard in their head. Whilst tinnitus is typically non-vascular, the vascular noises perceived by patients are bruits or pulsatile tinnitus.

5.4.2 *Cause of clinical event*

Every clinical event recorded is attributed to a patient. Each is also attributed to, where appropriate, a single brain AVM, a single aneurysm, a procedure complication, some other mechanism, or declared of an unknown aetiology.

Usually there is no doubt that a brain AVM caused a clinical event, for example a radiographically demonstrated ICrH in the same area of the brain in the absence of any other cause. In other cases, the radiological appearances of the ICrH and the morphology of aneurysms associated with the brain AVM are sufficient to attribute the haemorrhage to an associated aneurysm, rather than to the brain AVM nidus. This may be difficult with distal and nidal aneurysms (6.2.3, page 145), but may be easier with locations more distant from the nidus. The closer an aneurysm is to the nidus, the less clear this distinction becomes. If there is any doubt, the clinical and radiological details are independently reviewed by the SIVMS principal investigator, and if doubt remains the bleed is attributed to the brain AVM.

When there is uncertainty about whether a brain AVM or aneurysm caused an event or not, the attribution is 'unknown'. Headache is probably the most problematic of the clinical events in terms of determining its nature from case notes and interpreting whether it is attributable to a brain AVM or not. Without exception, the attribution of the headache – no matter what type – is unknown, pending satisfactory case-control studies demonstrating a clear association between brain AVMs and headache. The aetiology of cognitive impairment is similarly labelled 'unknown'. If brain infarction or

any type of FND is referable to the anatomic location of the nidus, its aetiology is attributed to the AVM, but if not it is labelled 'unknown'.

Occasionally, clinical events occur that could be construed as being due to a brain AVM, but they are probably not. For example, a patient has focal motor seizures, but the motor activity is ipsilateral to the brain AVM, which is very unlikely to be the cause; equally, a patient has an ICrH but it occurs contralateral to the AVM. In these circumstances, the event is recorded, independently reviewed by another SIVMS investigator and – depending on the clinical probability – either attributed to the AVM, 'unknown' causes, or 'other' causes if they clearly exist (which may be described in a free text box).

Clinical events that are *clearly* related to an intervention (e.g. haemorrhage *during* embolisation or surgical excision, or hair loss *following* embolisation/coiling) and occur within 30 days of it are attributed to a 'procedure complication'.

5.4.3 *Timing of clinical events*

5.4.3.1 Presentation (inception)

The date of the symptom onset that directly lead to a medical evaluation that in turn prompted investigation and a subsequent brain AVM diagnosis – known as the date of presentation – is the point of 'inception' in SIVMS, from which prospective follow-up starts. I supposed that little time would elapse between this date of 'presentation' and the date of 'diagnosis' (3.2.3.5, page 101) (when investigations either diagnose or raise the suspicion of a brain AVM). I also supposed that the diagnosis first coming to light would prompt notification of the patient to SIVMS, so that data collection from case notes would occur close to the date of first presentation, and so inception would truly mark the point from which prospective follow-up starts in the study.

Even if the event that prompted the investigation leading to brain AVM diagnosis was not symptomatic of the brain AVM, the date of this clinical presentation – albeit leading to an incidental discovery of the brain AVM – is the point of inception in the study.

Where the date of symptom onset is unknown, the date of the medical evaluation that led to diagnosis is regarded as the date of presentation.

Whereas the Joint Writing Group suggests the documentation of all symptoms occurring at presentation, SIVMS differs from it by allocating only one type of clinical event to presentation. For example, the co-occurrence of ICrH, an epileptic seizure and headache would simply be recorded as ICrH by SIVMS, because all else is symptomatic of it.

5.4.3.2 Symptoms prior to inception

The identification of symptoms occurring long before inception is usually made retrospectively from the past history of previous clinical encounters documented in the case notes, or the patient describes these symptoms at the time of presentation when a history is taken. Because I did not interview every person in SIVMS, the occurrence of these events is likely to have been underestimated. Nevertheless, SIVMS records these events because they provide an indication of the burden a brain AVM *may* have inflicted during the patient's lifetime.

5.4.3.3 Symptoms during follow-up/outcomes

Follow-up starts at inception and ends when a patient dies. Before death, the period of follow-up is derived from a variety of different fields in the database. The duration of follow-up is calculated from the most recent of the following dates: the date of the most recent clinic letter or discharge summary that SIVMS has managed to obtain from a patient's case notes, the date of completion of the most recent GP annual questionnaire, or the date of the most recently returned patient questionnaire.

During follow-up, various clinical events may occur either due to the brain AVM, associated aneurysm(s), or their treatment. An exact date is attributed to the *onset* of each clinical event (to enable time-dependent analyses), but an approximation (to the nearest day or month) is sometimes necessary when the three sources of follow-up information are imprecise. Information about these events is collated by the research fellow (myself 1999-2001) from the GP and hospital case notes, and GP and patient annual

questionnaires. As such, the assessment of outcome is independent of the clinicians directly involved in each patient's care in as much as the case notes give an independent account. However, the assessment is blinded to the morphological features of interest but not to the interventions a patient has received.

5.4.3.4 Death

Death marks the end of follow-up for every patient in SIVMS; in any other case follow-up is regarded as still underway. Death is either attributed to the brain AVM, associated aneurysm, a procedure complication, another cause, or unknown (and the source of this information is stored as one of the post mortem report, death certificate, or the case notes). In addition to the cause of death, information about its date and place, and whether a post mortem and/or neuropathology examination were performed are also recorded.

5.5 Summary

- Data about clinical events that affect study participants are derived from their hospital and GP case notes, follow-up GP questionnaires, hospital case notes surveillance, as well as questionnaires completed by the participants
- All clinical events that could possibly be related to a brain AVM are stored, whether they occurred at presentation (inception), prior to it (retrospective events), or during follow-up
- Clinical events are attributed to the brain AVM, an associated aneurysm, a procedure complication, another cause altogether, or unknown (when the brain AVM might have been responsible)
- The definitions used by SIVMS have external validity in the light of recent definitions proposed by the Joint Writing Group

5.6 Discussion

My approach to the categorisation and attribution of data has been reductionist. There are few certainties in clinical medicine, and especially not in the relatively unexplored area of brain AVMs. Whilst some events are certain (e.g. occurrence of ICeH in the same location as a brain AVM), others are less certain (e.g. whether rupture within the brain AVM nidus or an associated aneurysm caused the haemorrhage), and some are completely unknown (e.g. whether headaches are caused by brain AVMs). Other examples include the dilemma of whether a FND with perhaps mild headache and depressed consciousness for 24 hours without brain imaging is declared a 'FND' or a clinically probable 'haemorrhage'. By reflecting any (un)certainty in the way data are coded, I have made provision for ambiguities to be explored in sensitivity analyses.

The biases inherent in the way patients come to medical attention could be explored in a similar way, given the way data are stored. For example, in the interval between the date of presentation/inception (5.4.3.1, page 135) and the date of first definite brain AVM diagnosis by imaging or pathological examination (3.2.3.5, page 101), other clinical events may occur. The dilemma is whether the mode of presentation and these other events should be regarded as part of a patient's clinical course during prospective follow-up, or whether they are disregarded because the brain AVM diagnosis is not yet certain. Counting such events will tend to overestimate the aggressiveness of brain AVMs, yet reflect the character of those that do come to medical attention. Patients with less aggressive presentations may tend not to be investigated as thoroughly, or not investigated at all; this is evident amongst those who have apparently incidental brain AVMs, but examination of their medical history reveals retrospective events that – if investigated – might have led to brain AVM discovery. It is my personal opinion that the events between presentation and the time of definite diagnosis should be counted, because they do influence the way patients are managed, which is likely to affect prognosis. It will be of considerable academic interest, though, to describe clinical course both with and without these early events.

In Chapter 3 it was clear that my ascertainment of study participants is prospective, but that the retrieval of prior information about them is retrospective, occurring some time after the events in question. This is probably of little consequence, because the

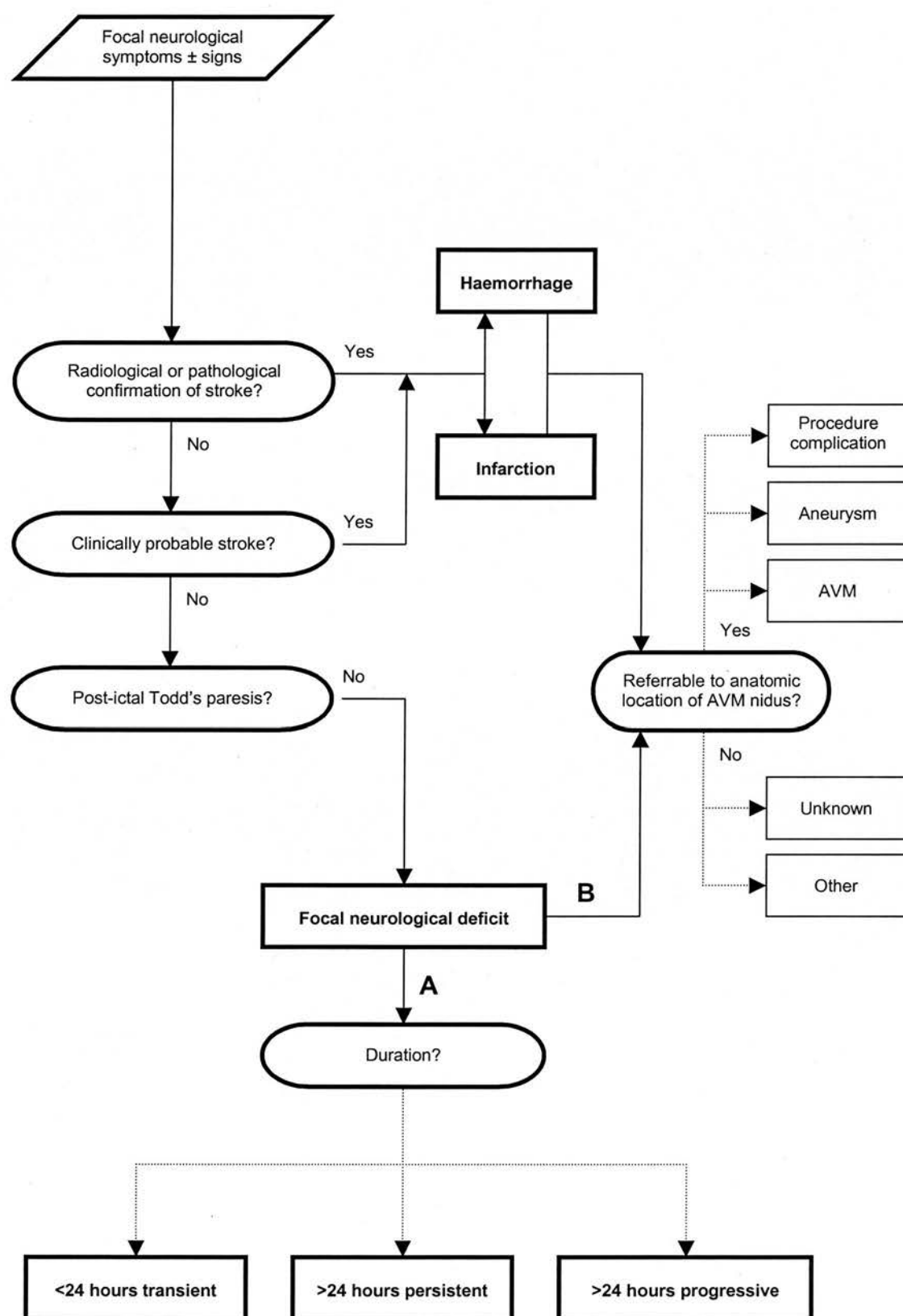
fundamental distinction between these two methods of data collection rests upon how likely an event is to be missed. Any events occurring prior to inception are best regarded as retrospective, because they depend on recall, the completeness of the GP record (and whether SIVMS has access to it), and their perceived importance (e.g. episodic migraine versus an isolated, unprovoked seizure, both without further investigation).

Whilst the accurate documentation of outcome events in clinical records is dependent on clinical acumen, adequate investigation, clear discharge summaries and bureaucratic efficiency, so too is it dependent on my judgement. My interpretation is most difficult when any of these attributes of adequate clinical records are missing, but my experience and education also influence it, and so too may my lack of blinding to certain features of interest. SIVMS has subsequently set up an outcome audit, whereby the study's principal investigator (Charles Warlow) categorises clinical outcomes, blinded to the research fellow's opinions as well as morphological features of interest and interventions received. Arguably, this should also be applied to clinical events at presentation. Thereby, a consensus of two opinions will hopefully result in a more accurate future analysis of prognosis.

Many of the fundamental clinical concepts are shared with the few other studies that have chosen to define them (e.g. NYIAVMS). However, SIVMS differs from other studies by striving to represent certain ambiguities, thereby being able to combine comparable data in any individual patient data meta-analyses, whilst also being able to explore the unknown biases of brain AVM clinical course using sensitivity analyses.

In the next chapter, I will describe the morphological attributes of brain AVMs themselves – whether identified by imaging or pathology – that have provoked so much interest as predictors of outcome.

Figure 11 Categorisation of focal deficits – including their duration (A) and their cause (B) – affecting patients with brain AVMs



Chapter 6. Morphological variables relating to brain arteriovenous malformations

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6.1 Introduction

Compared to the clinical characteristics covered in the preceding chapter, the morphological features of brain AVMs are likely to be the subject of as much – if not more – debate, and so observer variation (quantified in Chapter 10). The morphological variables of the majority of brain AVMs in SIVMS are collected whilst reviewing diagnostic imaging studies (performed prior to any treatment), although for some the only source of this information may be pathological examination. Although I clearly defined radiological variables that would be collected before SIVMS started, modifications were inevitable as my knowledge of brain AVMs grew and as concepts developed at brain imaging review meetings with the two study neuroradiologists. I have attempted to illustrate each radiological variable. As in the preceding chapter, I have highlighted areas where SIVMS's definitions deviate from those laid down by the Joint Writing Group and the NYIAVMS [Joint Writing Group 2001; Stapf *et al.* 2003].

6.2 General morphological variables

These variables describe attributes of brain AVMs that can be derived from radiological or pathological examinations. For exclusively radiological variables, see 6.3 (page 146).

6.2.1 *Side*

The side of a brain AVM refers to the laterality of its nidus. If the nidus involves a midline structure, yet it does not predominate on the left or the right, then it is deemed to be in the midline. For example, Figure 12 (page 160) illustrates a lateralised nidus (A), and another that involves midline structures, but predominates on one side (C).

6.2.2 *Location*

Brain AVM topographical location relates to the single anatomical structure in the brain that the majority of the brain AVM nidus occupies. Where two or more structures are equally involved, the most eloquent (6.4.1, page 155) of them is the allocated 'location'.

Existing terminology for the huge variety of brain locations is almost insufficient to classify nidi that often cross both anatomical and vascular boundaries, or have a diffuse margin (6.3.2, page 147). On the other hand, any attempt at simplification of the classification of location – to make grouping of lesions easier – could be seen as reductionist.

MRI and/or pathological examination are preferable to CT for the determination of brain AVM location; IADSA is the least desirable determinant of location, but it is rare for this to be the only diagnostic investigation.

Brain location of AVM nidus	
Frontal, frontoparietal, frontotemporal	Lobar
Parietal, parieto-occipital	
Temporal, temporo-parietal, temporo-occipital	
Occipital	
Basal ganglia	Deep
Thalamus	
Hypothalamus	
Corpus callosum	
Insula	
Internal capsule	Ventricular
Limbic	
Choroidal	Brainstem
Midbrain	
Pons	Cerebellar
Medulla oblongata	
Cerebellum (includes vermis, hemispheres and deep nuclei)	

Furthermore, the configuration of the brain AVM nidus in relation to the surface of its predominant brain area is specified, using information from MRI and/or IADSA and/or pathological examination (Figure 12, page 160). Where a detailed description of this configuration is not possible, the terms superficial or deep are used.

Configuration within brain area

Extracranial

Dural

Piocortical (sulcal)

Piocortical (gyral)

Piocortical (mixed)

Corticoventricular

Periventricular

Intraventricular

Superficial

Deep

SIVMS allocates a single brain location to each AVM, as others have done [Marks *et al.* 1990], but this differs from the Joint Writing Group's suggestion of specifying every location occupied by a brain AVM's nidus. My brain area categories are also more diverse than those used by the Joint Writing Group (cortical, basal ganglia, subcortical, internal capsule, ventricular, intraventricular, corpus callosum, cerebellar hemisphere, frontal, vermian (paramedian), temporal, deep cerebellar nuclei, parietal, brain stem, occipital), and the NYIAVMS (lobar: frontal, parietal, temporal, and/or occipital lobe; deep: basal ganglia, thalamus, internal capsule, corpus callosum; and/or infratentorial: midbrain, pons, medulla, cerebellum).

For each brain AVM, a determination of the 'eloquence' of its location is made, based on the Spetzler-Martin surgical grading scheme (6.4.1, page 155) [Spetzler and Martin 1986]. This anatomical scheme defined eloquent areas as: the sensorimotor (Figure 12A,

page 160; Figure 25B, page 173; Figure 26A, page 174), language and visual cortex (Figure 12D, page 160; Figure 25D, page 173); the hypothalamus and thalamus (Figure 12C, page 160; Figure 25C, page 173); the internal capsule; the brainstem (Figure 12C, page 160); the cerebellar peduncles and the deep cerebellar nuclei.

Naturally, the Spetzler-Martin determination of eloquence employed by both SIVMS and NYIAVMS is somewhat arbitrary; in contrast, the Joint Writing Group suggested that the basal ganglia should also be regarded as eloquent, in addition to 'other' sites (for example, non-dominant parietal lobe).

6.2.3 Associated aneurysms

An aneurysm is a focal luminal dilatation of a parent artery with a narrow neck or broad-based opening, visible on selective/non-selective IADSA and/or pathological examination, usually visible on CTA/MRA, and sometimes visible on plain CT and MRI. SIVMS does not classify large infundibula ($>3\text{mm}$) as aneurysms, although some research groups have done [Lasjaunias *et al.* 1988; Meisel *et al.* 2000], because they may be associated with brain AVMs [Miyasaka *et al.* 1982]. The NYIAVMS restricts its definition of aneurysms to those dilatations that are ≥ 2 fold larger than the diameter of their parent vessel.

Regardless of each aneurysm's mode of detection, SIVMS records its arterial territory (anterior cerebral, anterior communicating, middle cerebral, posterior cerebral, posterior communicating, vertebrobasilar, internal carotid), side (left/right/midline) and location in relation to the brain AVM nidus. 'Nidal' aneurysms originate from the vasculature of the nidus (although they may protrude beyond it), and should be visualised before the venous phase of IADSA (Figure 13C, page 161 and Figure 14A,B,D,E, page 162). 'Feeding artery' aneurysms are said to be 'proximal' if they reside on the supraclinoid internal carotid artery, on the circle of Willis, anywhere up to the middle cerebral artery bifurcation, anywhere on the anterior cerebral artery up to and including the anterior communicating artery, or on the vertebrobasilar trunk [Redekop *et al.* 1998]. Feeding artery aneurysms are 'distal' if they occur anywhere closer to the brain AVM nidus than the proximal locations (Figure 13A,B,D, page 161 and Figure 14C, page 162). Aneurysms are 'remote' if they are not associated with feeding or nidal vessels, but

occur in locations elsewhere, typical of sporadic aneurysms (Figure 13E, page 161 and Figure 14F, page 162).

If detected by IADSA, aneurysm morphology (saccular, fusiform, or ruptured), and aneurysm luminal diameter (in millimetres) are recorded. If any observed aneurysms are false aneurysms or pseudoaneurysms, this is recorded in free text boxes.

The Joint Writing Group differs from SIVMS by also stating whether aneurysms associated with brain AVMs are ‘flow-related’ or not. Furthermore, the Joint Writing Group suggests documenting whether and when an associated aneurysm has bled, but SIVMS records this separately from radiographic data, by attributing either aneurysm or brain AVM to a particular clinical event (5.4.2, page 134).

6.3 Exclusively radiological variables

Some features are reported for the brain AVM(s) demonstrated by every diagnostic imaging study performed on each patient. Brain AVM nidus side and location are stored only once and they are determined by the patient’s imaging study that is best suited to the task (6.2.1, page 142 and 6.2.2, page 142).

However, the following variables (sections 6.3.1, page 146 to 6.3.5, page 154) are recorded for every diagnostic imaging study (prior to treatment) that visualises the brain AVM. The final determination of what characteristic an individual brain AVM has for each of these variables is made by comparing the results of all the patient’s imaging studies, with some being preferred because they are the ideal modality for that characteristic and others rejected because they do not provide adequate information.

6.3.1 *Nidus size*

Nidus size has been the subject of great interest in many studies of brain AVM prognosis and treatment, although its accurate and consistent measurement is plagued by several difficulties. The definition of a nidus as the area towards which multiple feeding arteries converge and from which enlarged veins drain is somewhat arbitrary. Measurement of the entire nidus’ maximum linear diameter in each of three dimensions

is complicated by diffuse nidus types (6.3.2, page 147 and Figure 17, page 165). Furthermore, brain AVMs are commonly supplied by more than one vascular territory, which can prevent complete visualisation of the entire nidus when injecting a single vascular territory during IADSA. Neither consistent magnification factors nor calibrated markers are in frequent use [Pott *et al.* 1992]. Moreover, there are different methods of calculating size, including the maximum linear diameter in any dimension (when authors' interpretations of 'small' may be anything less than between 2cm and 3.5cm), and various volume calculations dependent on assumptions about the approximate shape of the nidus [Pasqualin *et al.* 1991; Soderman *et al.* 2000].

In SIVMS, brain AVM nidus size is measured as its maximum linear diameter in each of three dimensions (vertical, anteroposterior and transverse) which are measured in millimetres using any type of imaging. For measurement, MRI is preferable to CT, which in turn is preferable to IADSA. Ideally transverse, coronal and sagittal views should be available on MRI/CT, although some vertical dimensions are roughly estimated from the slice thickness on axial imaging when sagittal and/or coronal views are unavailable (Figure 15, page 163 and Figure 16, page 164). When nidus size is estimated from IADSA, the study radiologists used the diameter of the genu of the petrous portion of the internal carotid artery (5mm) as a reference [Paullus *et al.* 1977]

6.3.2 *Nidus morphology*

The nidus itself is usually compact – the arteriovenous tangle adopts a tightly packed spherical/elliptical configuration with a clear demarcation between nidus and neighbouring brain parenchyma (Figure 17, page 165 and Figure 12B,D, page 160). Occasionally the nidus border is diffuse, with a more irregular boundary interspersed with, or engulfing, islands of brain parenchyma (Figure 18A-C, page 166) [Chin *et al.* 1992]. Superselective IADSA has revealed the diversity of arteriovenous shunts within the nidus, from a simple fistula to a complex plexus [Houdart *et al.* 1993].

Pure arteriovenous fistulae do not have a nidus as such, but it is usually possible to visualise the fistula on IADSA. Sometimes a fistula is also discernible within a nidus as rapid shunting through a direct arteriovenous communication early in the angiographic

study (Figure 18D, page 166) [Marks *et al.* 1990], although its visualisation can be dependent on the use of superselective IADSA (Figure 18E, page 166).

6.3.3 *Arterial feeders*

There are usually several tortuous, branching, high flow arterial vessels of varying calibre and wall thickness that supply the central nidus where arteriovenous shunting occurs through one or more fistulae. These afferent vessels are typically recruited from more than one intracranial branch of the internal carotid and/or vertebrobasilar systems, and occasionally from branches of the external carotid or vertebral arteries through transdural anastomoses [Miyachi *et al.* 1993].

IADSA alone determines which vessels are seen to enter and feed (contribute flow to) the nidus. Feeding vessels are subdivided according to their side of the brain (left/right/midline), their arterial territory of origin (see overleaf), and the number of feeders supplied by each territory (Figure 18D,E, page 166 and Figure 19, page 167); ≥ 9 feeders implies multiple, uncountable branches (Figure 24A, page 172). Because arterial feeders may terminate in the nidus, continue to supply brain beyond the nidus (giving 'transit' – also known as 'en passage' supply) (Figure 18E, page 166 and Figure 21B, page 169), or arise indirectly from an artery in close proximity to the nidus, each is separately classified (terminal, transit, terminal & transit, pseudoterminal, indeterminate).

Arterial territory

Internal carotid

Anterior cerebral

Middle cerebral

Posterior cerebral

Vertebrobasilar

Anterior communicating

Posterior communicating

Lenticulostriate

Thalamoperforating

Dural

The Joint Writing Group suggests using a more detailed array of arteries (external carotid branches, internal carotid penetrators, other internal carotid branches, anterior choroidal, posterior choroidal, anterior cerebral cortical branches, anterior cerebral penetrators, middle cerebral cortical branches, middle cerebral penetrators, posterior cerebral cortical branches, posterior cerebral penetrators, basilar penetrators, vertebral branches, vertebral penetrators, superior cerebellar, anterior inferior cerebellar, posterior inferior cerebellar, other).

6.3.3.1 Arterial tortuosity

Arterial tortuosity of feeding arteries is subjectively graded (none, mild, moderate, severe) by comparing the vessel in question with the comparable contralateral vessel (Figure 20A, page 168).

6.3.3.2 Arterial angiopathy

Chronic high blood flow in the feeding arteries is thought, by some, to cause stenotic (Figure 21A, page 169) and/or dilated (Figure 21A, page 169; Figure 25B, page 173; Figure 26B, page 174) arterial ‘angiopathy’ due to endothelial thickening and intimal hyperplasia [Pile-Spellman *et al.* 1986]. Arterial angiopathy is subjectively graded (none, dilated, stenosed, dilated & stenosed) by comparing the feeding artery in question with the comparable contralateral vessel. Both the Joint Writing Group and NYIAVMS record the presence/absence of moyamoya-type changes in feeding arteries, by which they mean any pattern of collateral small-vessel recruitment resulting from proximal feeding artery occlusion or near-complete stenosis [Montanera *et al.* 1990]. This pattern includes recruitment of collateral supply to compensate for the occluded or stenotic arterial segment. Although SIVMS does not explicitly record this characteristic, it would be possible to detect brain AVMs that might have it by reviewing those with both arterial angiopathy and collateral supply.

6.3.3.3 Collateral supply

Collateral supply refers to arterial inflow supplying the high flow, low resistance nidus and/or brain distal to the AVM. This supply originates from anastomoses with dural (Figure 20C&D, page 168 and Figure 26B, page 174) or leptomeningeal (Figure 20B, page 168 and Figure 22, page 170) arteries supplying adjacent vascular territories, or between pedicles within the same vascular territory. This is also known as ‘non-sprouting angiogenesis’. It is recorded as being present (dural, leptomeningeal, unclear), absent, or uncertain.

6.3.3.4 Angiogenesis

Sprouting angiogenesis (Figure 21C&D, page 169) on IADSA represents anomalous arterial vessels feeding the nidus from arteries that are not usually expected to supply the territory occupied by the AVM nidus [Marks *et al.* 1990]. This is subjectively graded (yes/no/uncertain) by comparing the vessel(s) in question with the comparable contralateral vessel(s), although it can be hard to distinguish diffuse nidus morphology from sprouting angiogenesis (Figure 21D, page 169). Its correlate on MRI is perinidal

contrast enhancement. Neither the Joint Writing Group nor NYIAVMS record the existence of sprouting angiogenesis.

6.3.4 *Draining veins*

One or more dilated veins originate deep within the brain AVM nidus, and reach its surface acquiring tributaries along the way to drain, directly or via collateral pathways, into the superficial and/or deep venous systems (Figure 23, page 171). Through the loss of the normal resistance to flow in the capillary bed, the arteriovenous shunt transmits arterial pressure to the compliant venous system, causing venous hypertension. The draining veins are often anomalous, due to haemodynamic stresses causing stenosis, ectasia and varix formation [Viñuela *et al.* 1985].

From IADSA alone, SIVMS attempts to describe the complex anatomy of the venous drainage from a nidus by recording the total number of draining veins exiting the nidus and the side (left, right, midline) and ultimate destination of each, whether deep (subependymal) or superficial (see table overleaf). This is derived from the concept that the nidus is divided into compartments, each with its own draining vein. However, the Joint Writing Group has an additional method of simplifying the complexities of venous anatomy, by also quantifying the total number of veins reaching a venous sinus.

Draining vein destinations	Depth
Superior cerebral veins	Superficial
Middle cerebral vein	Superficial
Inferior cerebral vein	Superficial
Cortical vein	Superficial
Vein of Labbé	Superficial
Vein of Trolard	Superficial
Superior sagittal sinus	Superficial
Transverse sinus	Superficial
Sigmoid sinus	Superficial
Occipital sinus	Superficial
Torcular Herophili	Superficial
Cavernous sinus	Superficial
Superior petrosal sinus	Superficial
Inferior petrosal sinus	Superficial
Internal jugular vein	Superficial
Marginal sinus	Superficial
Spinal veins	Superficial
Great cerebral vein of Galen	Deep (periventricular)
Internal cerebral vein	Deep (periventricular)
Basal vein of Rosenthal	Deep (periventricular)
Straight sinus	Deep
Inferior sagittal sinus	Deep

Amongst all these separate draining veins, sometimes there is, or is not (Figure 24B, page 172), a dominant draining trunk.

6.3.4.1 Pattern of venous drainage

The overall pattern of venous drainage is deemed to be superficial (Figure 23C, page 171 and Figure 24C, page 172), deep (to the periventricular system) (Figure 23B, page 171 and Figure 24B, page 172), deep (but not to the periventricular system) (Figure 24A, page 172), or both deep and superficial (Figure 23A, page 171 and Figure 24B, page 172). Superficial drainage is defined as being exclusively through the cortical venous system, or to cerebellar hemispheric veins that drain directly into the straight sinus, torcula or transverse sinus. Deep drainage occurs through the deep cerebral veins, such as the internal cerebral veins, basal veins or precentral cerebral vein (above). This classification is also derived from the Spetzler-Martin grading scheme [Spetzler and Martin 1986] (6.4.1, page 155), with the additional subdivision of deep drainage according to whether it is subependymal/periventricular or not.

6.3.4.2 Other venous characteristics

SIVMS also records other attributes of venous angioarchitecture of the brain AVM as a whole, rather than of each individual draining vein. If there is any evidence of venous stenosis (narrowing of a draining vein in comparison to the vein proximal to it) then its degree is recorded (percentage reduction in the maximum proximal diameter at the narrowest portion) as is its location (at a dural sinus, or elsewhere) (Figure 23D&E, page 171 and Figure 24C, page 172). The degree of stenosis is at best an approximation because the measurements are close to the limit of resolution of IADSA films. The Joint Writing Group requires that venous stenosis be visualised in two different angiographic views, although these have rarely been available in SIVMS, so I have not used this criterion. One research group has recorded the existence of venous stenosis without a degree [Mansmann *et al.* 2000], whilst others have required a $\geq 50\%$ reduction in calibre to qualify as stenosis [Marks *et al.* 1990; Nataf *et al.* 1998]. Venous ectasia is defined as dilatation of a whole draining vein, when compared with surrounding veins (being distinct from focal stenosis) (Figure 23D, page 171 and Figure 24A, page 172). Whilst

SIVMS records venous ectasia as yes/no/uncertain and does not quantify it, the Joint Writing Group and NYIAVMS require a >2-fold calibre increase, although another group has stipulated that it only relates to segmental dilatations [Nataf *et al.* 1998]. SIVMS also records the presence of venous varices (yes, no, uncertain), which are aneurysmal dilatations or pouches on draining veins [Wallace and Bourekas 1998; Willinsky *et al.* 1988] (Figure 24D, page 172), whilst NYIAVMS and the Joint Writing Group do not, presumably – like others [Viñuela *et al.* 1987; Turjman *et al.* 1995a] – regarding them as part of the same phenomenon as venous ectasia.

If the brain AVM is anatomically close to a dural venous sinus, then the side and sinus on IADSA are recorded, as is whether it is occluded by anything other than arachnoid granulations (narrowed, patent, or occluded). Dilation or thrombosis of a sinus adjacent to the nidus are also recorded on CT or MRI.

The Joint Writing Group records the existence of venous reflux (the reversal of flow in any venous outflow pathway, in a direction away from the closest venous sinus), a subject of other research groups' interest too [Nataf *et al.* 1998; Mansmann *et al.* 2000], but SIVMS does not record it (Figure 23E, page 171).

6.3.5 *Other information*

Other information of interest is stored in a free text field, to identify whether extra angioarchitectural information was gleaned from super-selective angiography and assist retrospective identification of interesting cases.

Because endovascular catheters with pressure-monitoring devices are not in routine (or research) use in Scotland, intravascular pressure measurements are not recorded, although they are recommended by the Joint Writing Group (but not intended to be construed as a standard of clinical care).

6.4 Composite variables

6.4.1 Spetzler-Martin grade

This grading system was designed for the prediction of the risk of morbidity and death from operative treatment, according to particular characteristics of a brain AVM [Spetzler and Martin 1986]. A brain AVM is graded based on the maximum diameter of its nidus (6.3.1, page 146), pattern of venous drainage on IADSA (6.3.4.1, page 153), and the neurological eloquence of adjacent brain (see below).

Size of AVM	
small (<3cm)	1
medium (3-6cm)	2
large (>6cm)	3
Eloquence of adjacent brain*	
not eloquent	0
eloquent	1
Pattern of venous drainage [†]	
superficial only	0
deep	1
Grade = Total of scores	

* Eloquent = sensorimotor, language and visual cortex; hypothalamus and thalamus; internal capsule; brainstem; cerebellar peduncles; and deep cerebellar nuclei

[†] Superficial = cortical venous system & cerebellar hemispheric veins (that drain directly into the straight or transverse sinuses)

6.5 Complications viewed on CT and MRI

6.5.1 *Acute/new haemorrhage*

Acute haemorrhage is defined as fresh blood of high density on CT, or high signal methaemoglobin on T₁-weighted MRI. Diagnostic CT/MRI at or close to the time of presentation may reveal acute haemorrhage, in which case its type (5.4.1.1, page 129), side (6.2.1, page 142) and predominant intracranial location (6.2.2, page 142) are specified. These data provide radiological support for the clinical data about haemorrhage at presentation or during follow-up, and the radiological data are associated with these clinical events in the database.

The Joint Writing Group also suggests recording the estimated age and size of such haemorrhages, but SIVMS does not do this.

6.5.2 *Prior/old haemorrhage*

The occurrence of prior haemorrhage from a brain AVM is inferred on CT by calcification in the surrounding brain parenchyma (unrelated to the vasculature of the brain AVM), and on MRI by the presence of haemosiderin (and perhaps methaemoglobin). This is simply recorded, and may correspond with knowledge about clinically evident haemorrhages prior to inception in SIVMS, in which case these retrospective events are associated with the diagnostic imaging study.

The Joint Writing Group also infers prior haemorrhage from encephalomalacia adjacent to the nidus and/or the incidental discovery of haemosiderin at the time of surgical resection, but SIVMS does not. They also attempt to age prior haemorrhage, which SIVMS does not.

6.5.3 *Other features and potential complications*

The existence of the radiological appearances of brain infarction – ‘low density without mass effect’ on CT or ‘infarction’ on MRI – as well as its side (6.2.1, page 142) and

location (6.2.2, page 142) are recorded. On either imaging modality, the appearances of mass effect and hydrocephalus are recorded – whether due to the brain AVM or not – as are oedema related to the AVM nidus, vessel calcification on CT, and gliosis on MRI. These features are not mentioned in the Joint Writing Group or NYIAVMS variable lists. SIVMS records radiological and/or clinical (5.4.1.6, page 133) evidence of infarction because of the uncertain relationship between brain AVMs and infarction. SIVMS records mass effect and hydrocephalus as an indication of haemorrhage severity, and oedema and gliosis because they may reflect other ways in which brain AVMs cause symptoms.

6.6 Summary

- SIVMS has a minimum morphological dataset for brain AVMs, specifying the location and side of the brain the nidus resides in, as well as the presence of any associated aneurysms (identified by radiological or pathological examination)
- Other attributes of the arterial feeders, nidus and draining veins are only described if brain/vascular imaging is adequate to characterise them
- Composite variables, such as the Spetzler-Martin surgical grade, may be derived if adequate data are available from pathological and/or radiological investigation
- The definitions used by SIVMS have reasonable external validity in the light of recent definitions proposed by the Joint Writing Group, the latter being more specific
- The retention of hard copies of every participant's imaging in the SIVMS library will enable *post hoc* exploration/re-categorisation of angioarchitecture

6.7 Discussion

Great interest has been shown in the morphology of brain AVMs, perhaps because this has been the fundamental basis for their distinction from other IVMs, but also because

morphology is the most tangible – and therefore easiest – way to attempt to explain the heterogeneity of brain AVMs. It is telling that from my systematic review (Chapter 2) there are far more studies exploring the retrospective association of morphological variations with modes of presentation than there are good prospective studies of prognosis.

The core morphological dataset in SIVMS comprises those features likely to be available in the majority of cases, whether diagnosed by brain and vascular imaging or pathological examination. All of these features – side and location within the brain, and associated aneurysms – sadly, are arbitrary to varying extents. The nidus of a brain AVM may be irregular, vary in size, and involve several lobes of the brain thereby complicating the allocation of a single side and location. I may have over-simplified the determination of location by choosing one area only, but this will make data analysis easier. In my choice of a single area, I have chosen the most ‘eloquent’ area colonised by the AVM nidus. Eloquence itself is a rather arbitrary concept, defined by Spetzler and Martin (6.4.1, page 155) according to anatomical locations whose damage would cause disabling and obvious post-operative deficits (since functional MRI is not in routine use). The presence of aneurysms associated with brain AVMs may be identified by pathological examination, or any form of brain imaging from CT to IADSA, although IADSA is essential for their characterisation.

Many of the other detailed features of angioarchitecture are also dependent on the use of IADSA, but they are also susceptible to the technical limitations of the procedure, often incomplete recording of every view on hard copy, and observer variation in IADSA interpretation. For example, in routine clinical practice it seems that sizing markers are used infrequently during IADSA for the measurement of nidus size, and magnification errors are often not calculated (although a coin applied to the patient’s head is occasionally used as a surrogate marker). The volume of irregular nidi is difficult to determine, but can be derived from the maximum diameters recorded in three orthogonal planes, using a simple formula with assumptions about nidus shape [Pasqualin *et al.* 1991].

In the same way that SIVMS has stored complete paper copies of all case notes and extracted data currently thought to be relevant, copies of all available diagnostic imaging have been archived and morphological attributes currently thought to be relevant are

extracted. Just as for clinical data, the strength of this approach lies in the ability to refer back to the source data to validate abstracted variables, reclassify features when/if definitions change, and later collect other variables not originally thought to be pertinent. I imagine this approach is just as vital for morphological data, which are just as likely to be susceptible to observer variation, reclassification and post hoc collection as hypotheses develop.

Whilst a film-based archive of diagnostic radiological data is most convenient and familiar to radiologists, the source data are susceptible to degradation by manual handling and vulnerable to loss. Therefore, a digital archive would be an ideal storage medium for these valuable data, and furthermore it could enable more accurate measurement of, for example, nidus size and it could be easily and cheaply duplicated for distribution in observer variability studies (Chapter 10).

Figure 12 Laterality and location of brain AVMs

A: coronal T1-weighted MRI demonstrates a corticoventricular brain AVM clearly lateralised to the left parietal lobe.

B: sagittal T1-weighted MRI shows a superficial, frontoparietal picrocortical (gyral) brain AVM.

C: axial proton density MRI reveals a brain AVM deep in the midbrain, predominating in the right thalamus.

D: sagittal T1-weighted MRI demonstrates a superficial, parieto-occipital picrocortical (sulcal) brain AVM.

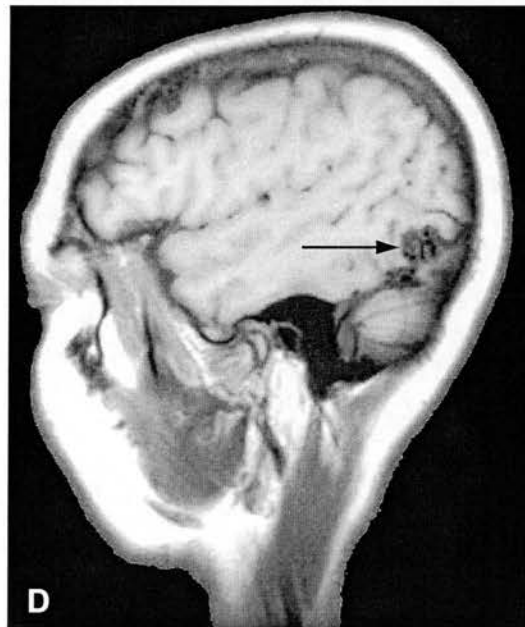
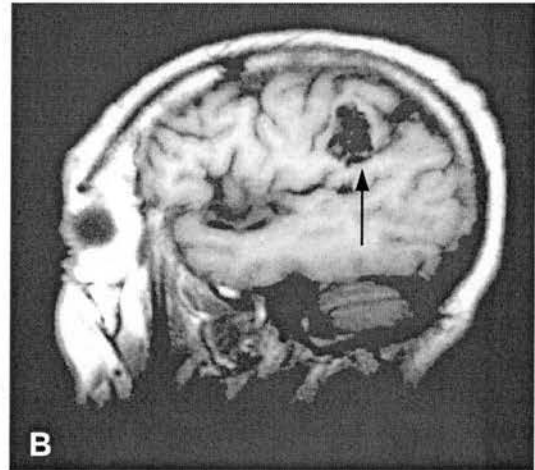


Figure 13 Classification of aneurysms, illustration from [Joint Writing Group 2001]

A and B: distal flow-related aneurysms

C: nidal aneurysms

D: proximal flow-related aneurysm

E: remote aneurysm

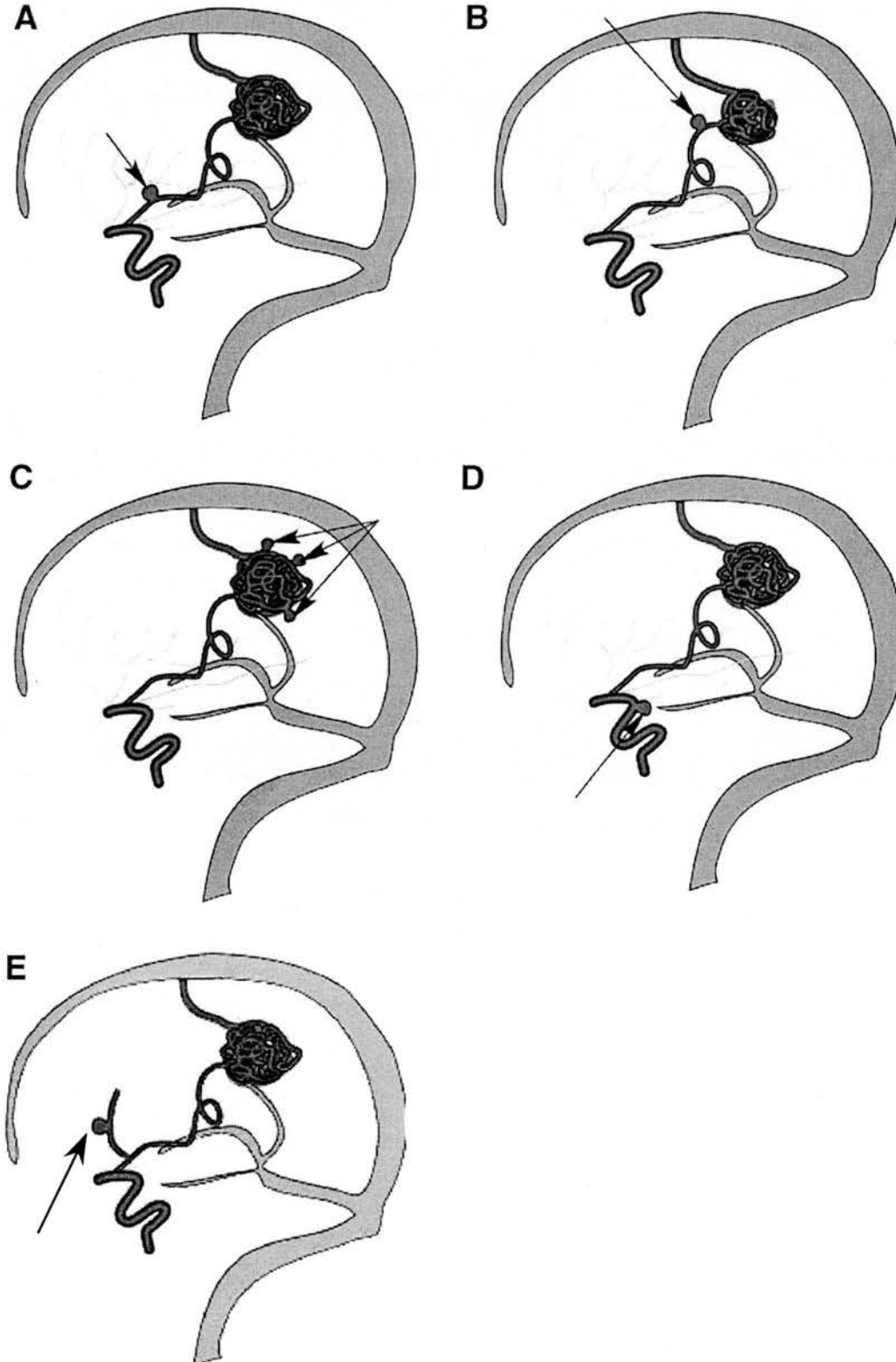


Figure 14 Aneurysms associated with brain AVMs, from SIVMS

A: a nidus with an unruptured nidus aneurysm. B: a nidus with an unruptured nidus aneurysm but multiple feeding artery aneurysms one of which had ruptured (C). D and E: a nidus with an unruptured 15mm nidus aneurysm on routine (D) and superselective angiography (E). F: an aneurysm remote from a brain AVM in the right temporo-parietal area

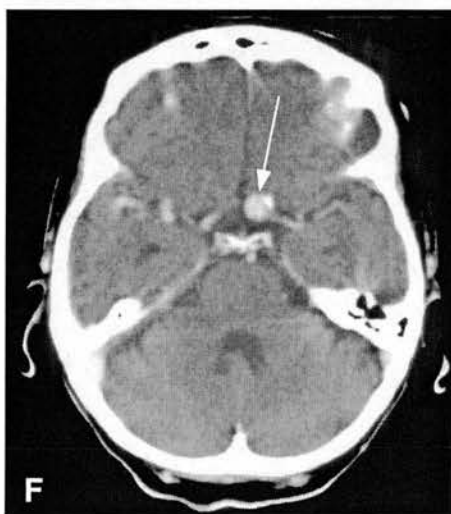
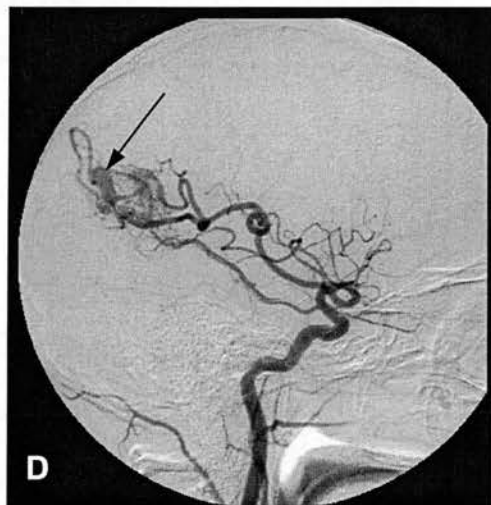
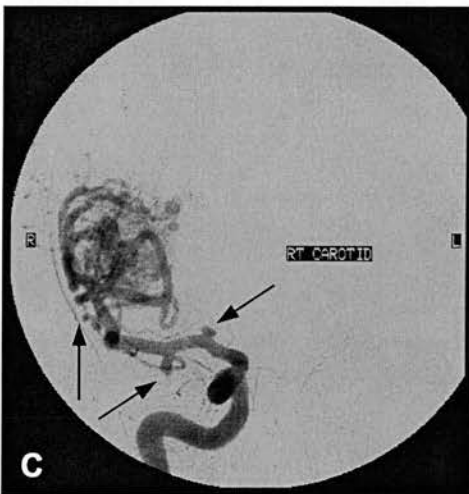
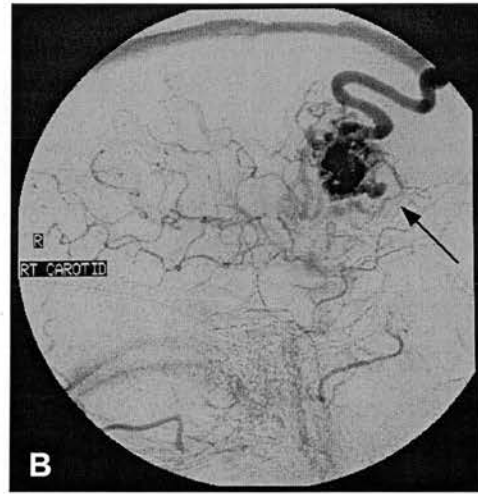
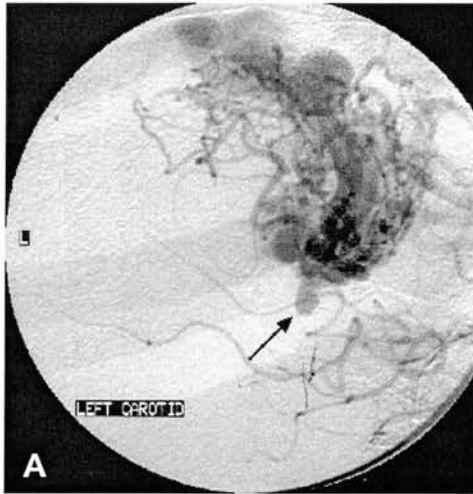
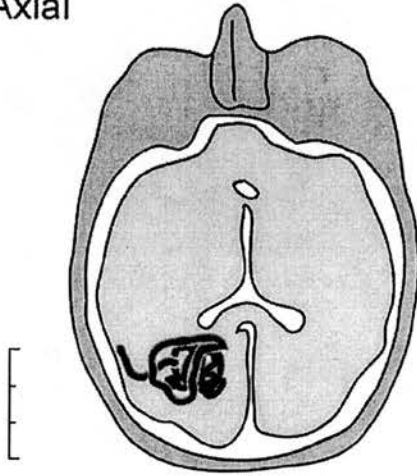


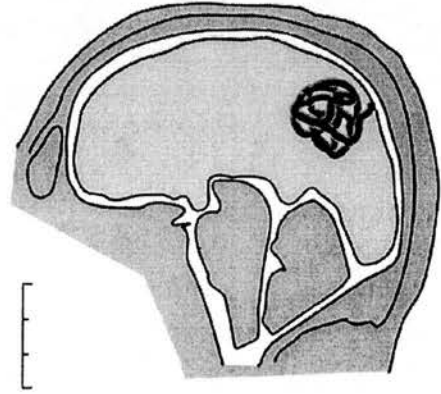
Figure 15 Size of brain AVM nidus on MRI, illustration from [Joint Writing Group 2001]

Each dimension can be measured on two views: transverse dimension from both axial and coronal views, anteroposterior dimension from axial and sagittal views, and vertical dimension from sagittal and coronal views (or by counting the number of axial slices on which the nidus appears)

Axial



Sagittal



Coronal

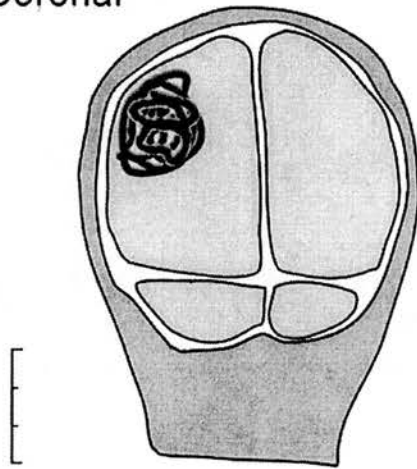


Figure 16 Size of brain AVM nidus on IADSA, illustration from [Joint Writing Group 2001]

Measurement of transverse (x), vertical (z) and anteroposterior (y) dimensions from anteroposterior (A-P) and lateral angiographic views

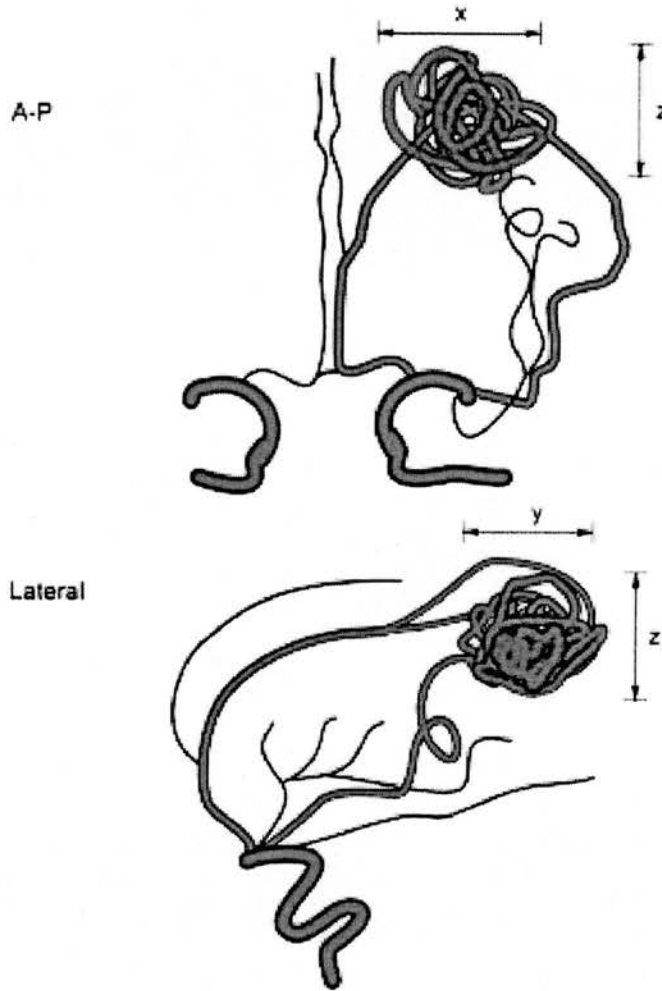


Figure 17 Nidus morphology, illustration from [Joint Writing Group 2001]

- A:** Compact nidus border
B: Diffuse nidus border

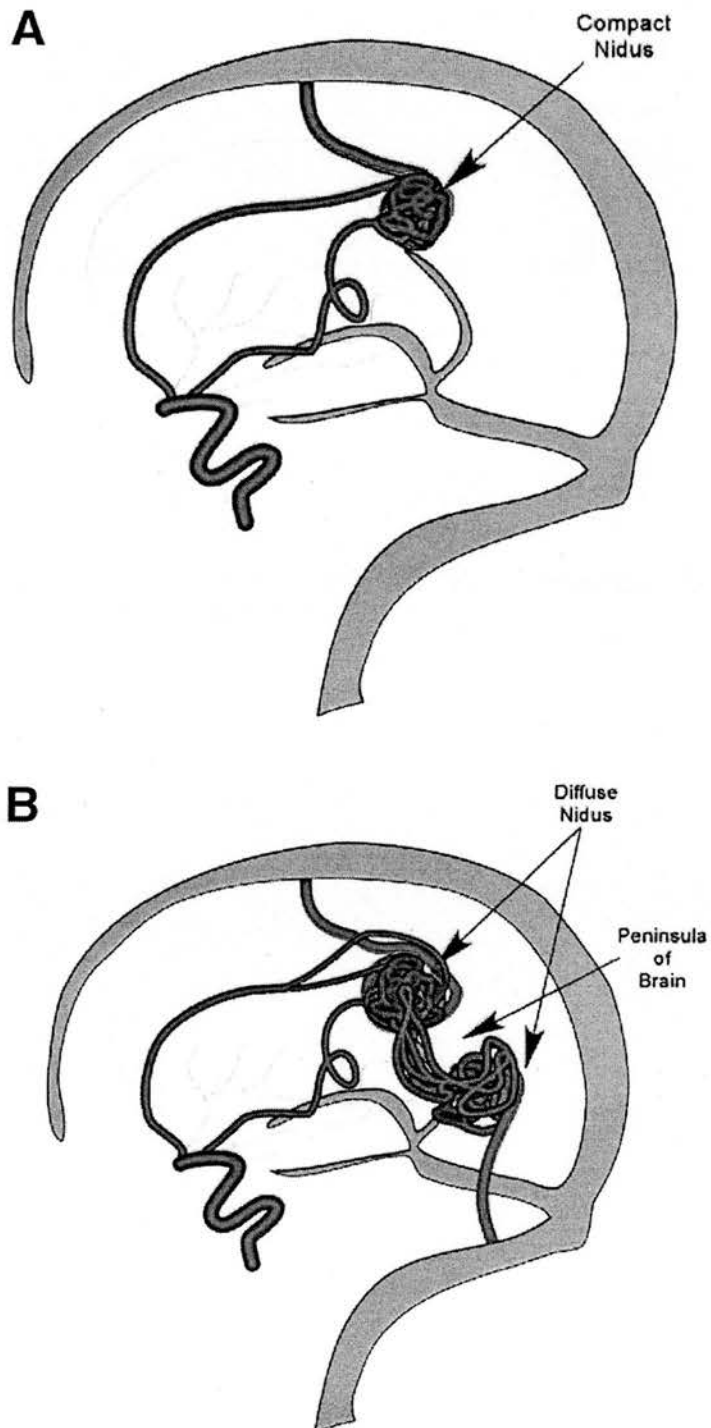


Figure 18 Nidus morphology, illustrations from SIVMS

A-C: Diffuse nidus. **D and E:** Arteriovenous fistula (solid arrow) with a single terminal feeder (dashed arrow) (D), but a second feeder giving en passage / transit supply (long dashed arrow) revealed by superselective IADSA (E).

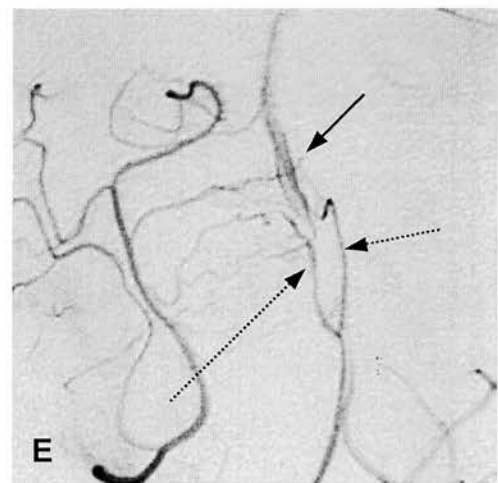
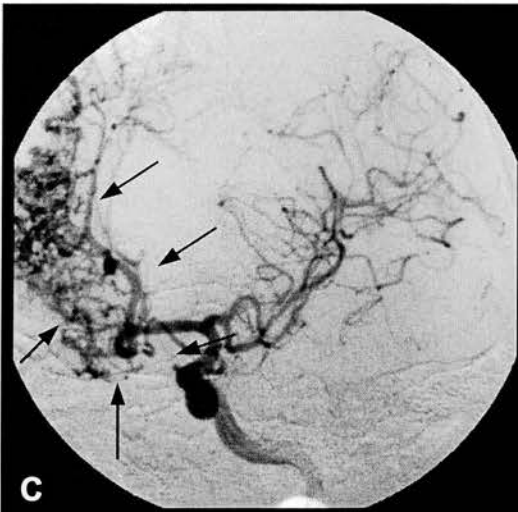
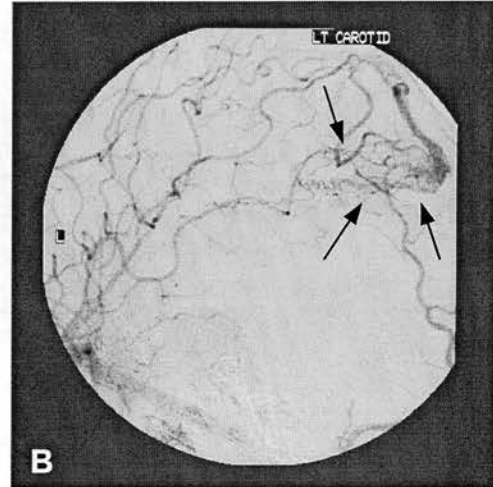
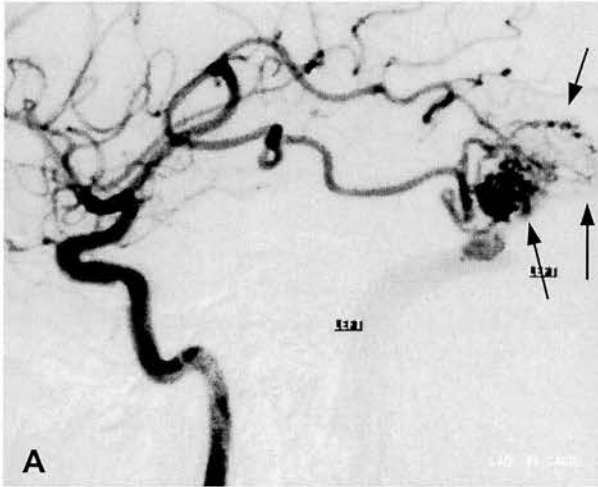


Figure 19 Multiple feeders, illustration from [Joint Writing Group 2001]

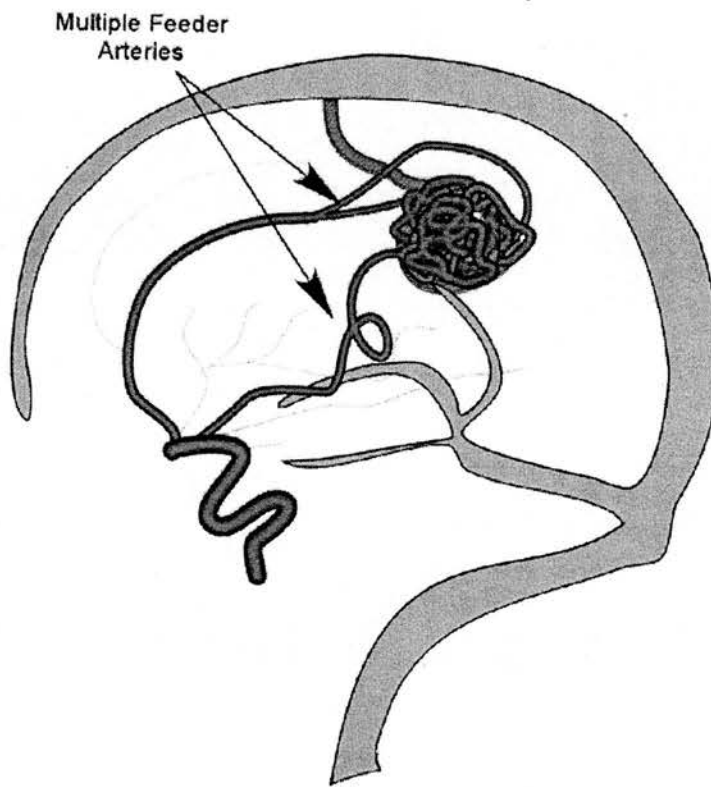


Figure 20 Variants of arterial angioarchitecture, from SIVMS

A and B: a right occipital brain AVM nidus, with moderate arterial tortuosity of 5 feeders from the posterior cerebral artery (arrows) visible on a lateral view of a right vertebral injection (A), with 3 middle cerebral artery leptomeningeal collateral feeders (arrows) revealed by an internal carotid artery injection (B).
C and D: a left temporal brain AVM nidus fed by terminal branches (arrow) of the left middle cerebral artery seen on a lateral view of a left internal carotid artery injection (C), with dural collateral supply from the middle meningeal branch of the left external carotid artery seen on a lateral view of a left external carotid artery injection (D).

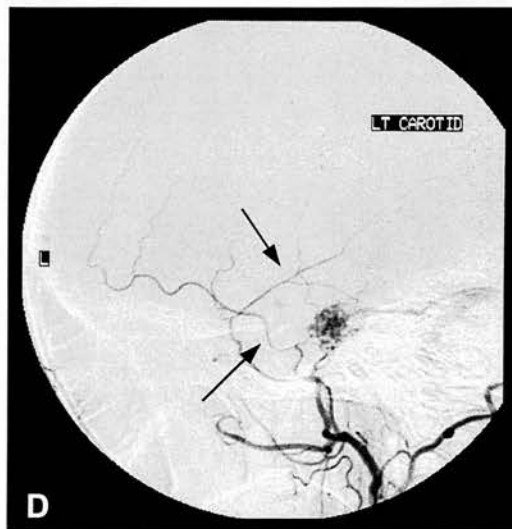
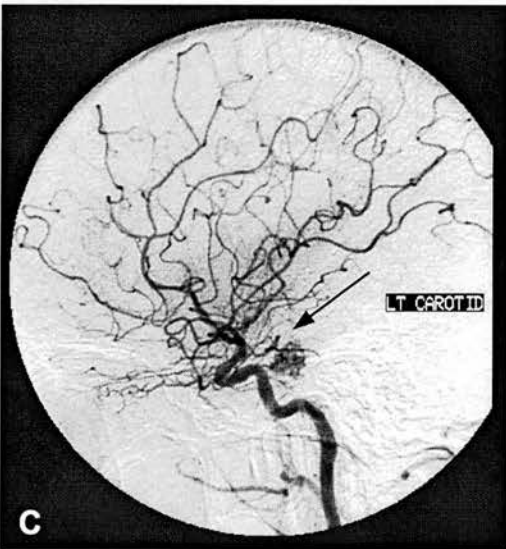
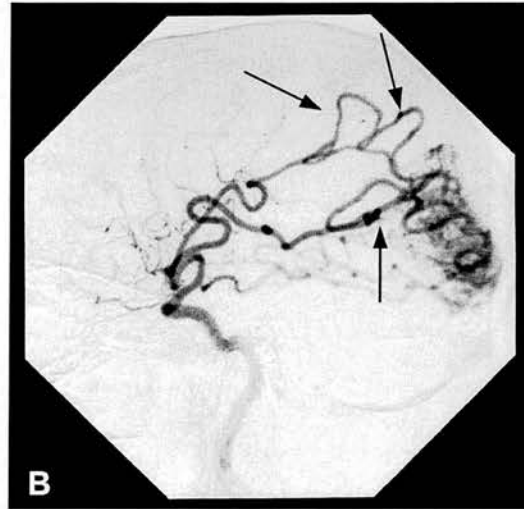
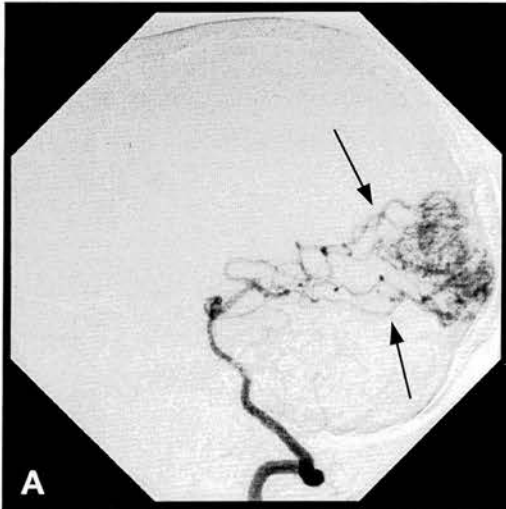


Figure 21 Variants of arterial angioarchitecture, from SIVMS

A: an anteroposterior view of a right internal carotid artery injection, demonstrating a right frontal brain AVM nidus, with arterial supply from the anterior and middle cerebral arteries, and evidence of both dilated (arrow) and stenosed (dashed arrow) arterial angioopathy.

B: a right occipital brain AVM nidus fed by terminal (arrow) and transit (dashed arrow) branches of the right posterior cerebral artery.

C: a right basal ganglionic brain AVM compact nidus (arrow), with dilated feeding artery angioopathy and sprouting angiogenesis (dashed arrows).

D: a right frontal brain AVM diffuse nidus, also with angiogenesis (arrows).

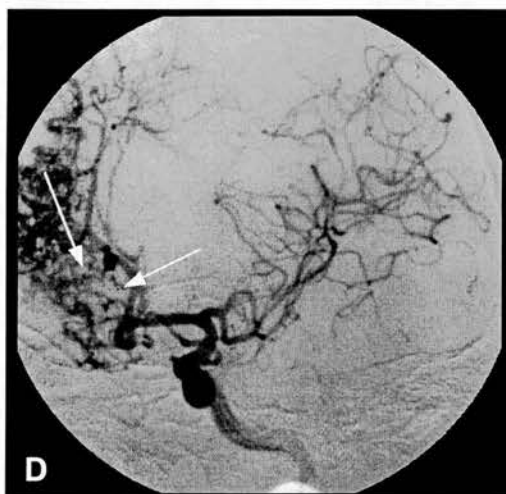
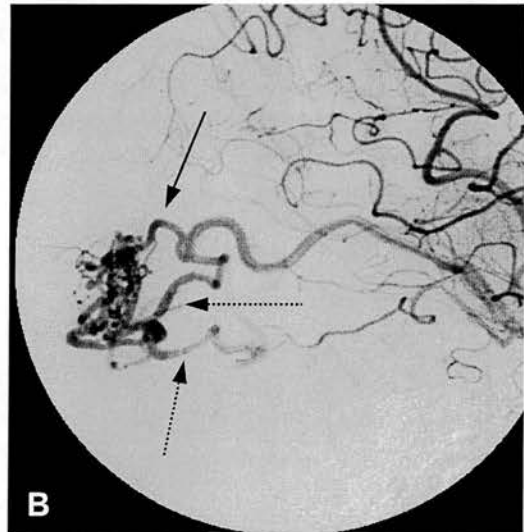


Figure 22 Leptomeningeal (pial-pial) collaterals, illustration from [Joint Writing Group 2001]

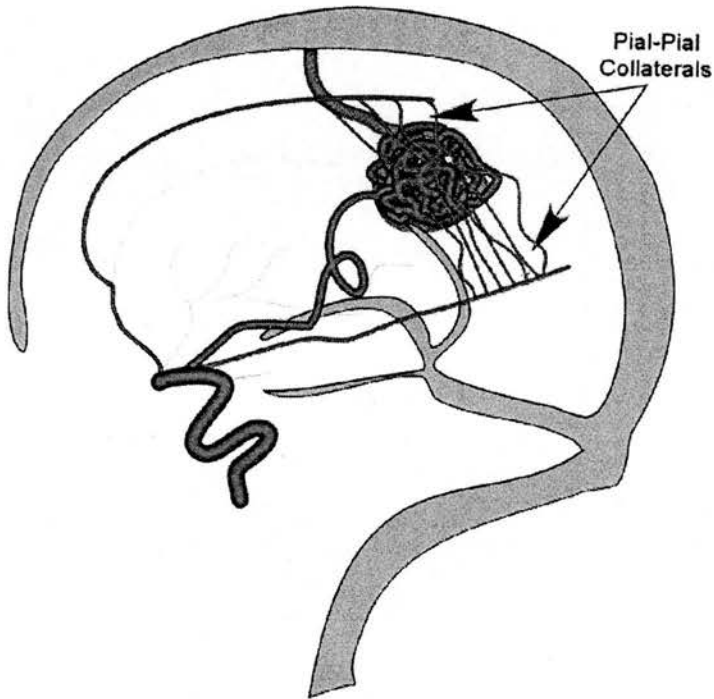


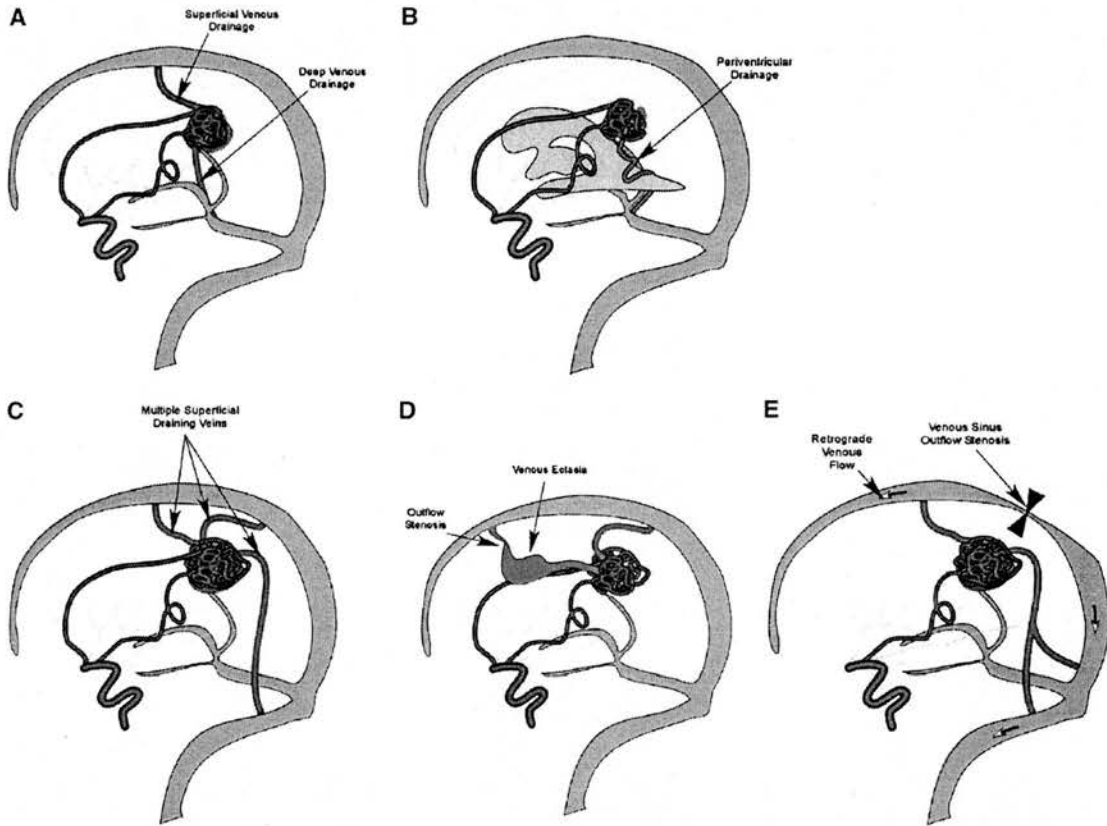
Figure 23 Venous drainage, illustration from [Joint Writing Group 2001]**A:** superficial and deep venous drainage.**B:** periventricular deep venous drainage.**C:** multiple superficial draining veins (3 vessels leave the nidus and 3 reach a sinus).**D:** venous ectasia and stenosis.**E:** retrograde venous flow (reflux) and outflow stenosis in sagittal sinus.

Figure 24 Venous drainage of brain AVMs

A: lateral IADSA of the vertebrobasilar system supplying the same brain AVM in Figure 12C (page 160) reveals multiple feeders, deep venous drainage to the Basal vein of Rosenthal (solid arrow), and venous ectasia (dashed arrow).

B: venous phase of a right internal carotid angiogram, demonstrating superficial venous drainage to the superior sagittal sinus (arrows) and deep periventricular drainage to the internal cerebral vein (dashed arrow), without a dominant draining trunk, from a compact right parietal nidus.

C: right parieto-occipital brain AVM nidus, with superficial venous drainage to the superior sagittal sinus, and 90% venous stenosis at the sinus (arrow).

D: left parieto-occipital brain AVM nidus, with venous drainage to the superior sagittal and transverse sinuses, and venous varices (arrow).

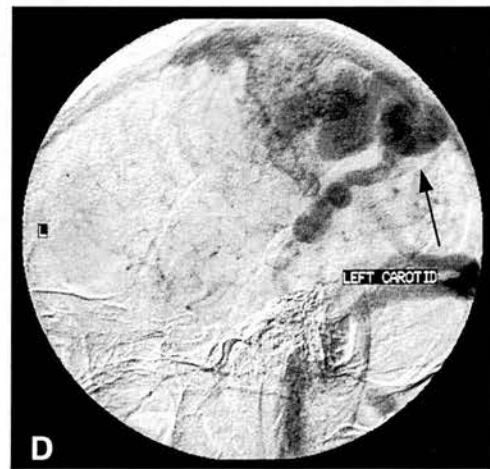
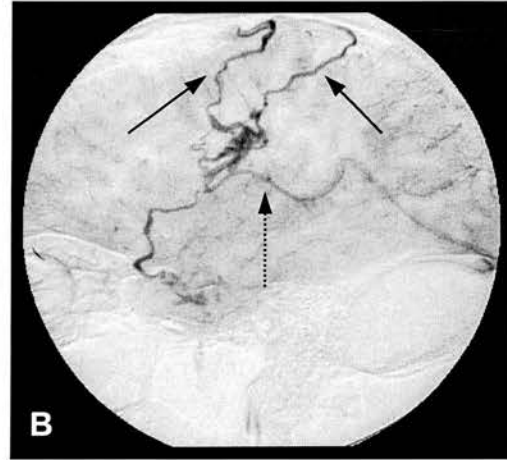
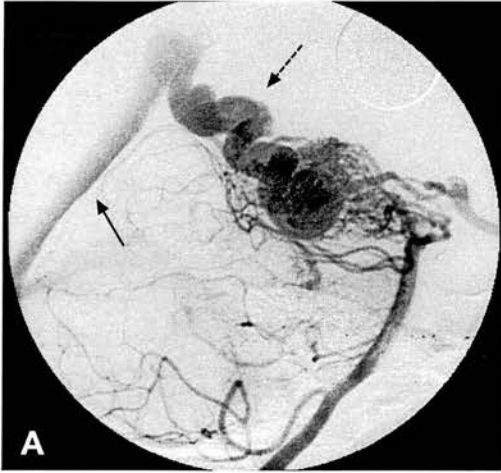


Figure 25 Spetzler-Martin grading scheme for brain AVMs

A: grade 1 small (7mm^3) brain AVM nidus (arrow) in the non-eloquent right temporal lobe with superficial drainage to a cortical vein.

B: grade 2 small brain AVF (large arrow) in the eloquent dominant frontoparietal cortex (motor strip), fed by the anterior cerebral artery (small arrow) and draining to the superior sagittal sinus.

C: grade 3 small (7mm^3) brain AVM nidus (arrow) in the eloquent right thalamus, which had venous drainage to both the right transverse (superficial) and straight (deep) sinuses (not shown).

D: grade 4 medium (30 mm^3) brain AVM nidus (arrow) in the eloquent right occipital lobe (visual cortex) with venous drainage to both the right transverse and superior sagittal sinuses (superficial), as well as the deep straight sinus.

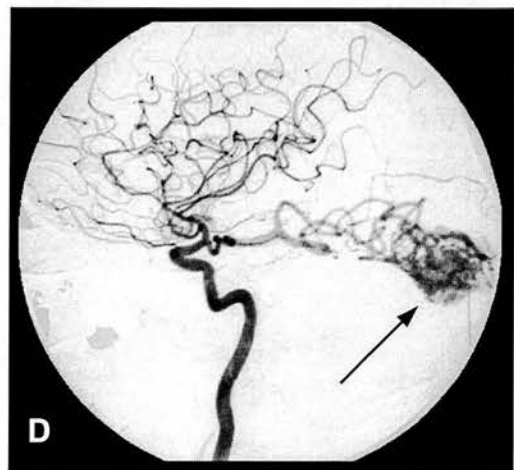
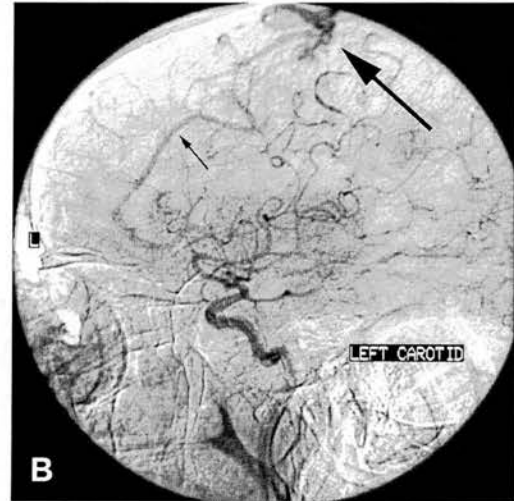
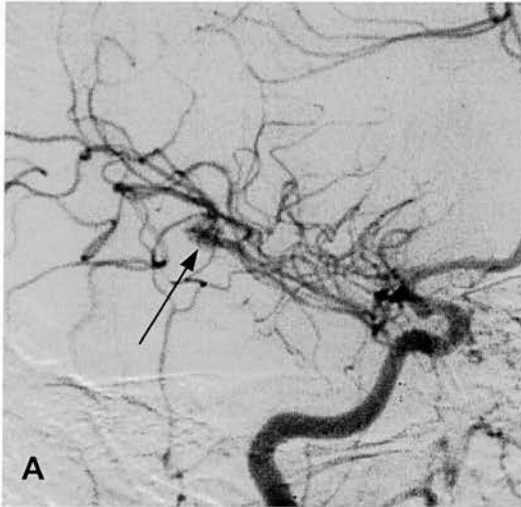
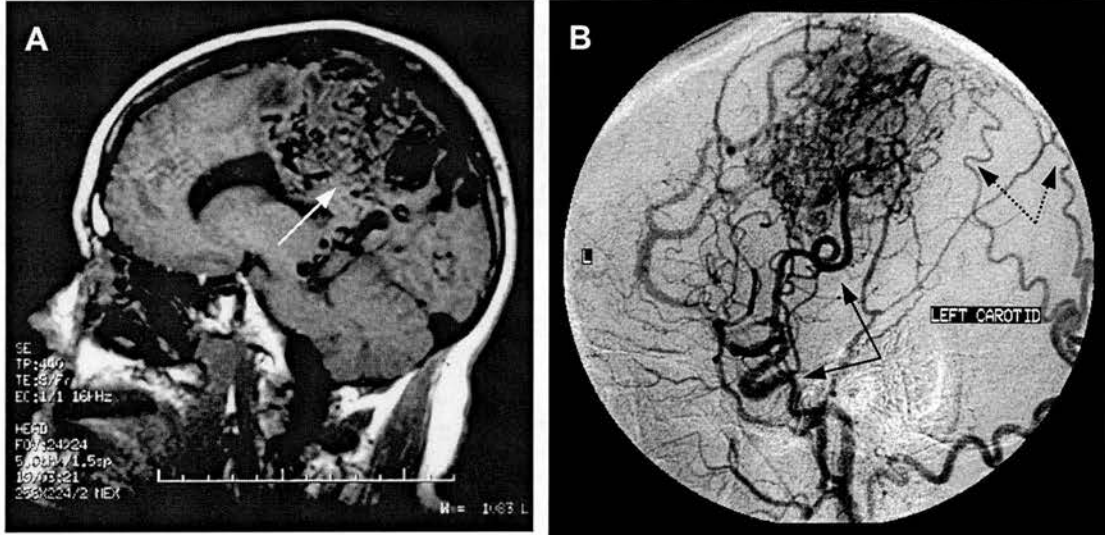


Figure 26 Spetzler-Martin grading scheme for brain AVMs

A and B: Grade 5 large (50 mm^3) brain AVM nidus (arrow) in a corticoventricular distribution in the eloquent left parieto-occipital area, with venous drainage to both the left transverse and superior sagittal sinuses (superficial), as well as the deep straight sinus.

B: dilated feeding artery angiopathy (solid arrows) and dural collateral supply (dashed arrows) are also evident on catheter angiography.



Section 3: The Scottish Intracranial Vascular Malformation Study (SIVMS) – evaluation of methods

- Chapter 7 The Scottish Intracranial Vascular Malformation Study (SIVMS) – data quality
- Chapter 8 The Scottish Intracranial Vascular Malformation Study (SIVMS) – evaluation of population-based design
- Chapter 9 The Scottish Intracranial Vascular Malformation Study (SIVMS) – evaluation of ICD-10 coding and potential sources of bias
- Chapter 10 Observer variation in the interpretation of catheter angiograms of brain AVMs

Chapter 7. The Scottish Intracranial Vascular Malformation Study (SIVMS) – data quality

Chapter contents

- 7.1 Introduction
- 7.2 Evaluation of completeness and progress with study recruitment
- 7.3 Quality of baseline clinical data
- 7.4 Quality of baseline diagnostic morphological data
- 7.5 Summary
- 7.6 Discussion

7.1 Introduction

Even if SIVMS realises the aspirations of section 2, its value will still depend on the quality of its data.

Sources of error causing poor quality data may be systematic or random. They can be categorised into data collection problems, data errors, and lack of quality improvement devices [Arts *et al.* 2002]. Various errors intrinsic to the data may occur due to ambiguous definitions, unclear guidelines for those inputting data, confusing data entry design, database programming errors, and incompleteness/unsuitability of the data source. Errors arising in data collection are attributable to non-adherence to definitions, typing/transcription errors, and insufficient data checks. Quality improvement schemes designed to minimise these errors include both quality assurance and quality control, occurring before and after data collection respectively.

Various database procedures were implemented as SIVMS started in order to prevent insufficient data quality (e.g. a minimum acceptable dataset for notification), detect imperfect data and their causes (e.g. queries checking appropriateness, completeness and inconsistencies in the data), and institute necessary corrective action (3.3, page 110). Furthermore, other checks occur after data collection to highlight problematic or inconclusive cases at the time of data analysis and these will be mentioned in Chapter 12.

I have taken a pragmatic view of the meaning of quality, viewing it as the characteristics of a data set that bear on its ability to satisfy the intended uses of the data. In this chapter I have described the quality of baseline variables in terms of:

- completeness, or the extent to which data are recorded for each variable, with $\leq 5\%$ the acceptable level for missing data
- range (upper and lower variable limits)

This process of evaluating important study variables (Chapter 19) is essential, prior to investigating in the next two chapters whether the study has achieved its desired aim of being representative of the Scottish population (Chapter 8) with minimal bias (Chapter 9).

7.2 Evaluation of completeness and progress with study recruitment

During 1999 and 2000 in Scotland – following independent review of case notes, brain imaging and pathological records – 96 adults were diagnosed with a definite, probable or possible brain AVM, and were therefore regarded as being ‘included’ in SIVMS. 45 adults were incident in 1999, and 51 were incident in 2000. Of these 96 adults, 92 harboured a definite brain AVM. Adults with a probable or possible brain AVM, which may subsequently become definite, are of equal interest to SIVMS and so worthy of active recruitment and participation in the study (described further in Chapter 13). Therefore, my interest in, and evaluation of, study recruitment applies to all 96 included adults (Table 12, page 182).

The progress of patients through SIVMS and the quality of their recruitment data are testament to the automated database processes that relentlessly press for data completeness, and the tireless efforts of the study secretary. All 96 patients’ GP and main hospital consultant are known. They tended to disagree more about whether SIVMS could contact patients by post (13%) than they did about whether the patient was aware of their diagnosis (2%). This was largely because of the contrasting perspectives of primary and secondary care: particular consultants felt certain patients should not be bothered and GPs generally felt every patient should be approached about their inclusion in a research study.

Of all 96 included patients, 85 (89%) were alive at the time of recruitment. Of these living patients, 73 (86%) were approached to join the study, of whom 69 (95%) returned their forms and consented (3% of whom declined to complete annual questionnaires). No one specifically declined to join the study, or denied access to their case notes.

GPs tended to express concern about SIVMS accessing notes when explicit consent had not been obtained from the patient, despite ethical approval having been given for this when consent was impossible/impractical. Ultimately 96% of GPs granted access to case notes, but because some required us to attend the practice to copy the notes (which I have not yet done), only 91% of them have been received. In contrast, access to case notes was granted by 99% of consultants at every hospital the patient had visited and

which held notes about them, and 99% of these notes have been received. 98% of diagnostic scans performed at these hospitals have also been received.

7.3 Quality of baseline clinical data

The patient group of interest for detailed description and analysis of baseline clinical and morphological data are those with a 'definite' brain AVM, so this and the following section on the quality of these data refer to the 92 such adults in the first 2 years of SIVMS.

Basic demographic data such as name, date of birth and gender are available for every patient (Table 13, page 183). Many other demographic details (for example, telephone number and next of kin), mainly useful for contacting and tracing the patient, are dependent on the study having obtained a baseline questionnaire, and therefore reflect the proportion who consented (72%). The study's high quality data for variables such as maiden name (also obtained by questionnaire) and CHI number (obtained from Practitioner Services) assist accurate record linkage by ISD. The comprehensive data about mode of presentation reflect the study's success in obtaining case notes. Information about family history primarily is drawn from the patient's baseline questionnaire, but exceeds its completion rate because the notes are sometimes enlightening too. The completeness of death certificate data reflects the ease of acquiring contemporary data from the GRO. However, the completeness of autopsy data disguises how difficult it was to obtain these reports (especially when the Procurator Fiscal had been involved) at a time when pathologists were guarded about releasing data because of the Alder Hey scandal.

7.4 Quality of baseline diagnostic morphological data

These data are obtained about brain AVMs and associated aneurysms from brain imaging, and occasionally only autopsy/biopsy (Table 14, page 184 and Table 15, page 185). Of all 92 adults with a definite brain AVM, 80 (87%) had ≥ 1 CT, 41 (45%) had ≥ 1 MRI, 68 (74%) had ≥ 1 IADSA, and 10 (11%) had a pathological examination of some sort (excision biopsy or autopsy). Amongst the imaging studies performed, a brain AVM

was visualised on only 61% of CTs, 77% of MRIs, and on all 68 IADSA. I have evaluated data completeness for all investigations performed, rather than per modality per patient, or per investigation on which a brain AVM was visualised.

From these investigations, complete data were available for the location of each brain AVM (Table 14, page 184). Although size measurements were available on 84% of all CTs, 94% of all MRIs and 93% of IADSAs, overall size in three dimensions was only available for 76 (83%) of the whole cohort.

Data quality was excellent (100%) for important attributes such as whether imaging revealed ICrH, but was poor for attributes perceived as less important, such as the state of adjacent venous sinuses (50% on CT and $\leq 34\%$ on IADSA) and venous stenosis (53% on IADSA).

7.5 Summary

- Baseline data quality in SIVMS is a reflection of study definitions, process and database procedures
- SIVMS maximises data quality by using clear definitions of clinical and radiographic variables, automatically checking minimum data provision and consistency at data entry, deliberately analysing for errors, and spotting outliers
- 89% of patients were alive at the time of recruitment, of whom 86% were approached to join the study, of whom 69 (95%) returned their forms and consented to join SIVMS (72% of the whole cohort)
- 96% of GPs granted access to case notes, but only 91% of them have been received; 99% of consultants granted access to case notes, and 99% of these notes have been received; 98% of diagnostic scans performed at these hospitals have been received
- Basic demographic data were present for every patient, and more detailed information were available if they consented
- Complete data were available for the location of each brain AVM, but size in three dimensions was available for only 83% of the cohort

7.6 Discussion

The existing data quality reflects the passage of time between the recruitment of the cohort and completing this thesis 5 years after the start of SIVMS. Disagreements (e.g. between GP and hospital consultant) early on in recruitment – although they usually result in the most conservative outcome – have been largely resolved, and variable completeness has been improved over time. Some data cannot be evaluated and are still dependent on thorough study process (e.g. ensuring SIVMS has recorded every hospital patient visits and so retrieved every imaging study).

Data accuracy (the extent to which the data conform to the truth) comprises validity, consistency and reliability. The main approaches to this are:

- range checks (to ensure that data outside a permitted range are not allowed)
- consistency checks (to ensure that the data make sense)
- external validation using an alternative source (for example, by auditing a random sample of study patients to ensure their baseline attributes and outcomes recorded in the database match the paper clinical record and questionnaires)

Whilst the first two approaches have been used, SIVMS has not yet been subject to the latter. This could be performed not only to validate existing paper records, but also by other researchers to assess inter- and intra-rater variation in the interpretation of case notes or imaging (Chapter 10). Prior to writing this thesis, I had produced draft guidelines for subsequent researchers to use for the interpretation of radiological data, but sadly these never benefited from peer review by the study neuroradiologists, so they are yet to be introduced. If any such innovations were to be used to improve data quality (perhaps not only of baseline variables, but also of outcomes), I would intend to conduct pre- and post- assessments of quality to quantify their impact.

Table 12 Study recruitment: completeness of variables and progress
 Data on completeness and/or measures of study progress (where applicable) from 96 included adults with a definite (92), probable (1), or possible (3) brain AVM, first diagnosed 1999-2000
 N/A = not applicable

	Completeness (%)	Progress, n (%)
Patient's GP's identifier	96 (100)	N/A
Patient's main consultant's identifier	96 (100)	N/A
Does the GP think the patient is aware of their diagnosis?	96 (100)	N/A
Does the main consultant think the patient is aware of their diagnosis?	96 (100)	N/A
GP and main consultant disagree about awareness	N/A	2 (2) disagree; 94 (98) agree
Overall decision about patient's awareness of diagnosis	96 (100)	77 (80) aware
Does the GP think SIVMS can contact the patient by post?	96 (100)	75 (78) yes, 8 (8) unknown, 13 (14) no
Does the main consultant think SIVMS can contact the patient by post?	96 (100)	78 (81) yes, 4 (4) unknown, 14 (15) no
GP and main consultant disagree about postal contact	-	12 (13) disagree
Overall decision about postal contact with the patient	96 (100)	73 of 85 (86) living patients to be contacted
Patients replied to recruitment forms	-	69 (95) did, 4 (4) did not
Patients declined to join study	69 (95)	0 actively declined
Patient consented to SIVMS copying their notes?	68 (99)	68 (99)
Patient consented to receive questionnaires?	69 (100)	67 (97) consented, 2 (3%) declined
Does the GP grant access to the patient's notes?	96 (100)	92 (96) agree
GP case notes received?	92 (100)	84 (91) received, 7 (8) fetch
Hospital's identifier	190 (100)	N/A
Consultant's identifier	190 (100)	N/A
When case notes exist at a hospital, does the consultant grant access to them?	178 (100)	2 (1) decline
Where there's access, notes identification number	144 (81)	N/A
Notes received from each hospital?	178 (100)	176 (99) received
Scanned at this hospital?	190 (100)	158 (83) yes, 2 (1) unknown
If scanned, imaging identification number	92 (58)	N/A
Diagnostic scans received from each hospital?	216 (100)	211 (98) received

Table 13 Completeness of baseline clinical variables

Data on completeness and range of baseline demographic and clinical variables from 92 adults with a definite brain AVM, first diagnosed 1999-2000
N/A = not applicable

	Completeness, n (%)	Range
All patients (n=92)		
Title	92 (100)	N/A
Forename	92 (100)	N/A
Surname	92 (100)	N/A
Date of birth	92 (100)	31/01/1917 to 07/04/1984
Gender	92 (100)	See Chapter 13
Marital status	62 (67)	N/A
Maiden name (of 23 known to have been married)	21 (91)	N/A
Handedness	65 (71)	N/A
Ethnic code	65 (71)	See Chapter 13
CHI number	92 (100)	N/A
City	92 (100)	N/A
Post code	91 (99)	N/A
Telephone number	61 (66)	N/A
Email	4 (4)	N/A
Next of kin	64 (70)	N/A
Next of kin telephone number	59 (64)	N/A
Is there a family history of IVMs, or similar?	78 (85)	6 (7) may have FHx
First presentation date	92 (100)	23/11/1998 to 07/11/2000
First presentation type	92 (100)	See Chapter 13
Baseline Rankin score at presentation	92 (100)	See Chapter 13
Dead patients (n=13)		
Place of death	12 (92)	N/A
Cause of death	13 (100)	See Chapter 13
Source of information about cause of death	13 (100)	N/A
Death certificate obtained?	13 (100)	13 (100)
Post mortem examination performed (n=4)		
Where the examination was performed	4 (100)	N/A
Date of post mortem	4 (100)	N/A
Post mortem report received?	4 (100)	N/A

Table 14 Completeness of baseline morphological features of brain AVMs and their CT/MRI characteristics

Data from 92 adults with a definite brain AVM, first diagnosed 1999-2000

	Completeness (%)	Range
General AVM morphological attributes (n=92)		
Side of the brain	92 (100)	See Chapter 14
Brain area	92 (100)	See Chapter 14
Location within brain area	92 (100)	See Chapter 14
Eloquence of brain area	92 (100)	See Chapter 14
Spetzler Martin grade	71 (77)	See Chapter 14
CT attributes (n=112; 80 diagnostic, 32 follow-up)		
Intravenous contrast given?	86 (77)	30 yes, 56 no
Does the AVM enhance (of all given contrast)?	30 (100)	30 yes
AVM dimensions (AVM visible on 68 CTs)	57 (84)	See Chapter 14
Mass effect exerted by AVM?	112 (100)	50 yes, 59 no, 3 uncertain
Hydrocephalus?	112 (100)	28 yes, 81 no, 3 uncertain
Oedema around AVM?	70 (63)	9 yes, 59 no, 2 uncertain
Vessel calcification?	100 (89)	28 yes, 69 no, 3 uncertain
Calcification from old haemorrhage?	100 (89)	5 yes, 87 no, 8 uncertain
Acute haemorrhage?	112 (100)	62 yes, 50 no
Type of acute haemorrhage	62 (100)	See Chapter 13
Area of acute haemorrhage	55 (89)	See Chapter 13
Side of acute haemorrhage	51 (82)	See Chapter 13
Infarction?	100 (89)	8 yes, 92 no
Aneurysms visible?	86 (77)	4 yes, 82 no
Dilatation/thrombosis of adjacent venous sinus	56 (50)	1 yes, 44 no, 11 uncertain
MRI attributes (n=47; 41 diagnostic, 6 follow-up)		
Intravenous contrast given?	43 (91)	12 yes, 31 no
Does the AVM enhance?	11 (92)	8 yes, 2 no, 1 uncertain
AVM dimensions (AVM visible on 36 MRIs)	34 (94)	See Chapter 14
Mass effect exerted by AVM?	47 (100)	17 yes, 29 no, 1 uncertain
Hydrocephalus?	47 (100)	4 yes, 41 no, 2 uncertain
Oedema around AVM?	39 (83)	2 yes, 35 no, 2 uncertain
Gliosis around AVM?	35 (74)	9 yes, 25 no, 1 uncertain
Perinidal contrast enhancement?	10 (83)	1 yes, 6 no, 3 uncertain
Evidence of old haemorrhage	36 (77)	34 none, 2 some
Acute haemorrhage?	47 (100)	15 yes, 32 no
Type of acute haemorrhage	15 (100)	See Chapter 13
Area of acute haemorrhage	15 (100)	See Chapter 13
Side of acute haemorrhage	12 (80)	See Chapter 13
Evidence of infarction?	36 (77)	1 yes, 35 no
Aneurysms visible?	43 (91)	2 yes, 41 no

Table 15 Completeness of baseline angiographic features of brain AVMs and associated aneurysms

Data from 92 adults with a definite brain AVM, first diagnosed 1999-2000

	Completeness (%)	Range
IADSA attributes (n=68)		
Size	63 (93)	See Chapter 14
Arterial tortuosity	68 (100)	See Chapter 14
Arterial angiopathy	68 (100)	See Chapter 14
Angiogenesis	68 (100)	See Chapter 14
Arterial feeder source	108 (100)	ACA 26, dural 2, ICA 2, MCA 41, PCA 23, Pcom 1, vertebrobasilar 9
Side of arterial feeder	108 (100)	49 left, 2 midline, 57 right
Type of arterial feeder	99 (92)	72 terminal, 12 transit, 5 transit & terminal, 10 indeterminate
Quantity of branches from the feeder	108 (100)	1-9
Collaterals	68 (100)	See Chapter 14
Source of collaterals	10 (100)	See Chapter 14
Related to a dural sinus?	23 (34)	Limited categories
Side of this dural sinus	17 (25)	2 left, 2 right, 13 midline
State of sinus	22 (32)	17 patent, 3 occluded, 2 narrowed
Nidus border	62 (91)	See Chapter 14
Discernible fistula in nidus?	67 (99)	See Chapter 14
Number of draining veins	67 (99)	1-4
Venous drainage pattern	68 (100)	See Chapter 14
Dominant draining trunk	68 (100)	See Chapter 14
Draining vein destination	108 (99)	Limited categories
Draining vein side	106 (97)	67 midline, 22 left, 17 right
Venous varices	68 (100)	See Chapter 14
Venous ectasia	68 (100)	See Chapter 14
Venous stenosis	36 (53)	0-100
Are there aneurysms on the IADSA?	66 (97)	17 yes, 49 no
Aneurysm location	28 (100)	See Chapter 14
Aneurysm arterial location	21 (75)	Limited categories
Aneurysm artery side	21 (75)	8 left, 2 midline, 11 right
Aneurysm morphology	26 (93)	26 saccular
Aneurysm size	26 (93)	2-15mm

Chapter 8. The Scottish Intracranial Vascular Malformation Study (SIVMS) – evaluation of population-based design

Chapter contents

- 8.1 Introduction
- 8.2 Completeness of case ascertainment
- 8.3 Representativeness of the population
- 8.4 Summary
- 8.5 Discussion

8.1 Introduction

Whether or not the dataset for each patient is complete, SIVMS's exhaustive search for eligible adults would only be worthwhile if it resulted in a reasonably complete population-based sample. The more complete the sample, the more accurate the measured incidence will be. The more the sample is representative of the population as a whole, the more the results from SIVMS will be generalisable and have external validity.

8.2 Completeness of case ascertainment

Figure 27 (page 191) illustrates the overlap between the sources of ascertainment of brain AVMs. In the first year of the study, GPs only contributed cases already known to SIVMS, so this labour-intensive and ineffective exercise was abandoned in the second year. The widespread collaborative network identified the vast majority of adults, and there was ~50% overlap between the two major sources. Routine coding of hospital discharge and death certificate data (using I60.8 and Q28.2; see Table 11, page 115) identified the majority of adults who had died or been admitted to hospital. Coding failed to identify several adults who had only been seen as outpatients, but it did yield 4 adults (4% of the total) who were unidentified by the collaborative network.

8.3 Representativeness of the population

The adults incident in 1999 and 2000 were domiciled in proportion to the dispersion of the whole mid-2000 population estimate by health board (Figure 28, page 192), suggesting even ascertainment. Based on this dispersion of the cohort, there appeared to be mild over-ascertainment in the two Scottish health boards where specialist brain AVM clinics operate (Lothian and Greater Glasgow). However, the 95% confidence intervals of the age-standardised incidence ratios for each health board all overlapped 1 (Figure 29, page 193 and Figure 30, page 194), indicating that there were no detectable differences in ascertainment when the spread of the cohort was adjusted for the population of each health board (although the power to detect a difference was small).

8.4 Summary

- The optimal sources of case ascertainment were notifications from a multidisciplinary network of collaborators in the clinical neurosciences, supplemented by routine coding of hospital discharge and death certificate data
- There was ~50% overlap between these two sources
- The cohort was domiciled in proportion to the dispersion of the Scottish population
- Age-standardised incidence ratios did not suggest significant differences in ascertainment between health board areas

8.5 Discussion

In attempting to identify a complete sample representative of the population, SIVMS used several sources of case ascertainment. My pragmatic approach to assess the completeness of ascertainment was to observe the degree of overlap between the sources used (Figure 27, page 191). Whilst prospective identification of every adult by the two main sources – although impossible – would be extremely reassuring, the ~50% overlap is adequate. In the context of a country which – as yet – does not have routine coding of brain imaging and outpatient attendances, the study has achieved as thorough case ascertainment as is possible. Coding would never detect people diagnosed only as outpatients, although some may still be retrospectively ascertained in future years if they are admitted to hospital with epilepsy or ICrH, or for investigations or treatment, so the degree of overlap will increase over time.

Regional healthcare systems dictate which sources are most appropriate. I contemplated searching additional potential secondary data sources, including diagnostic radiology and pathology reporting systems in the geographical area of interest [Singh *et al.* 2000]. But when I surveyed these departments across Scotland I found that few had electronic reporting systems, and fewer still were searchable. There are few existing surveillance systems that might have provided a ready-made infrastructure for incident brain AVM detection. The British Neurological Surveillance Unit (BNSU) co-ordinated by the

Association of British Neurologists (www.theabn.org/academic/bnsu.html) is one such system. However, the disadvantage for SIVMS was that the BNSU only targets consultant neurologists, rather than all the specialists (and training grades) in the clinical neurosciences who might encounter patients with brain AVMs. I simply ensured that the study's collaborative network encompassed all consultant neurologists in Scotland known to the BNSU.

By using as broad a collaborative network as possible and aiming to recruit every incident adult with a brain AVM in the population, SIVMS has recruited what seems to be a population-based cohort. Of course, this may simply represent even under-recruitment across the country, but the similarity of the total number included in the first two years suggests not.

By being population-based, hopefully SIVMS will have quantified incidence accurately and so in its future analysis of prognosis it will avoid many of the disadvantages of hospital-based studies.

Hospital-based cohorts tend to represent local referral practices and the beliefs and treatment preferences of research groups with a special interest in brain AVMs, rather than describe the behaviour of a more representative population-based sample. Hospital-based studies are more likely to detect people with a disabling (yet non-fatal) mode of presentation, and if SIVMS had simply relied upon specialists it would probably have been biased towards people with more extensive investigation and treatment (Chapter 9). This hospital-based sampling bias also affects prognostic subgroups unequally, it makes the comparison of separate hospital-based cohorts inappropriate, and it militates against their meta-analysis. This has been confirmed by an analysis of five single centre brain AVM cohorts, which were found to have significant differences in both demographic and clinical characteristics as well as in brain AVM angioarchitecture [Hofmeister *et al.* 2000]. Comparison of such cohorts with SIVMS will be made later in this thesis (Chapter 13 and Chapter 14).

Figure 27 Sources of ascertainment of brain AVMs in the population of Scotland from the first (above) and second (below) years of the study

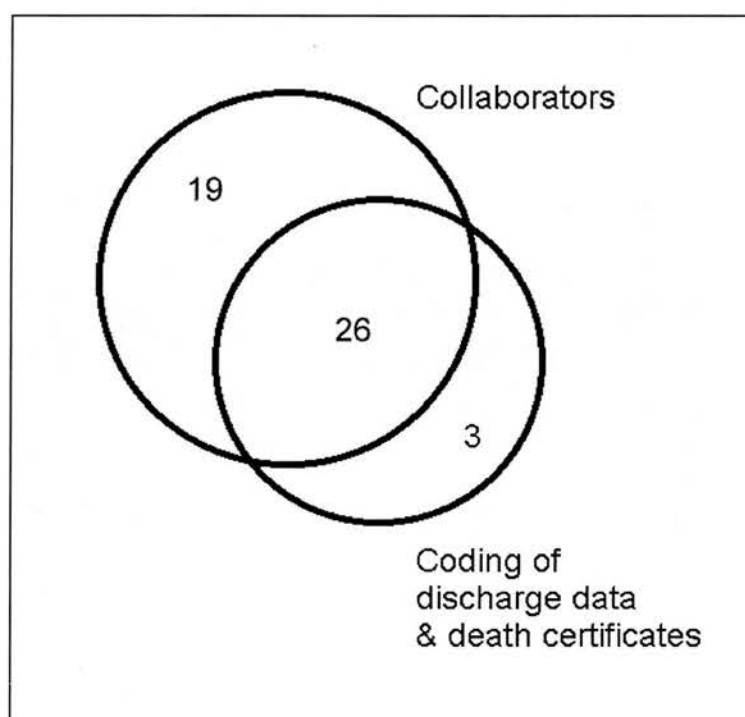
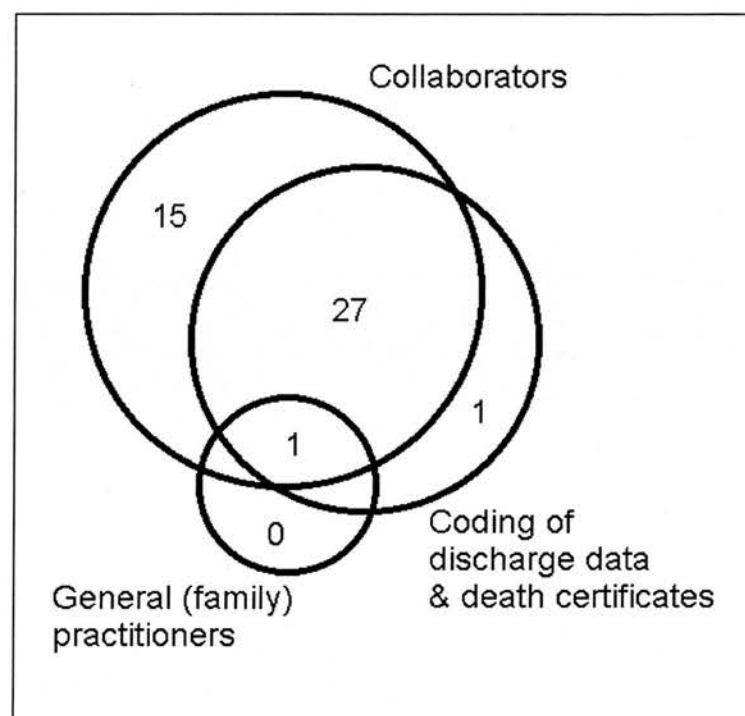


Figure 28 The percentage distribution (with 95% CIs) of adults with a brain AVM recruited to SIVMS in 1999-2000 by their health board of residence (white), compared with Scottish population density (black)

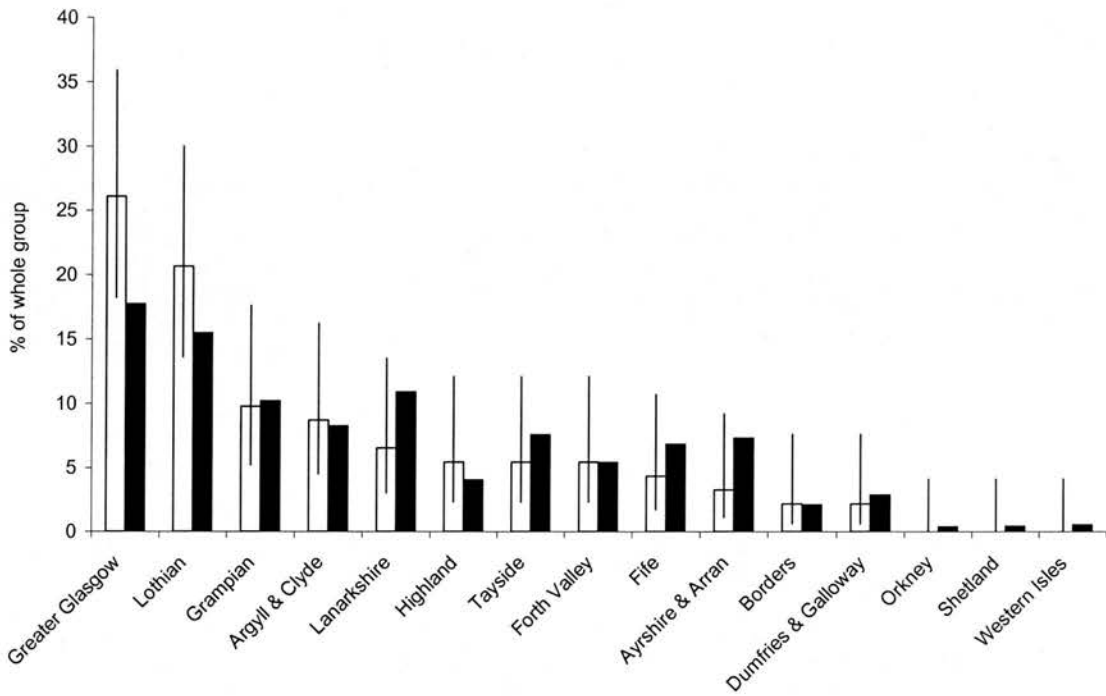


Figure 29 Age-standardised brain AVM incidence ratios for each of the 15 health boards in Scotland with 95% CIs.

The area of each point estimate is proportional to the age-standardised number of cases in each health board (arranged in descending order)

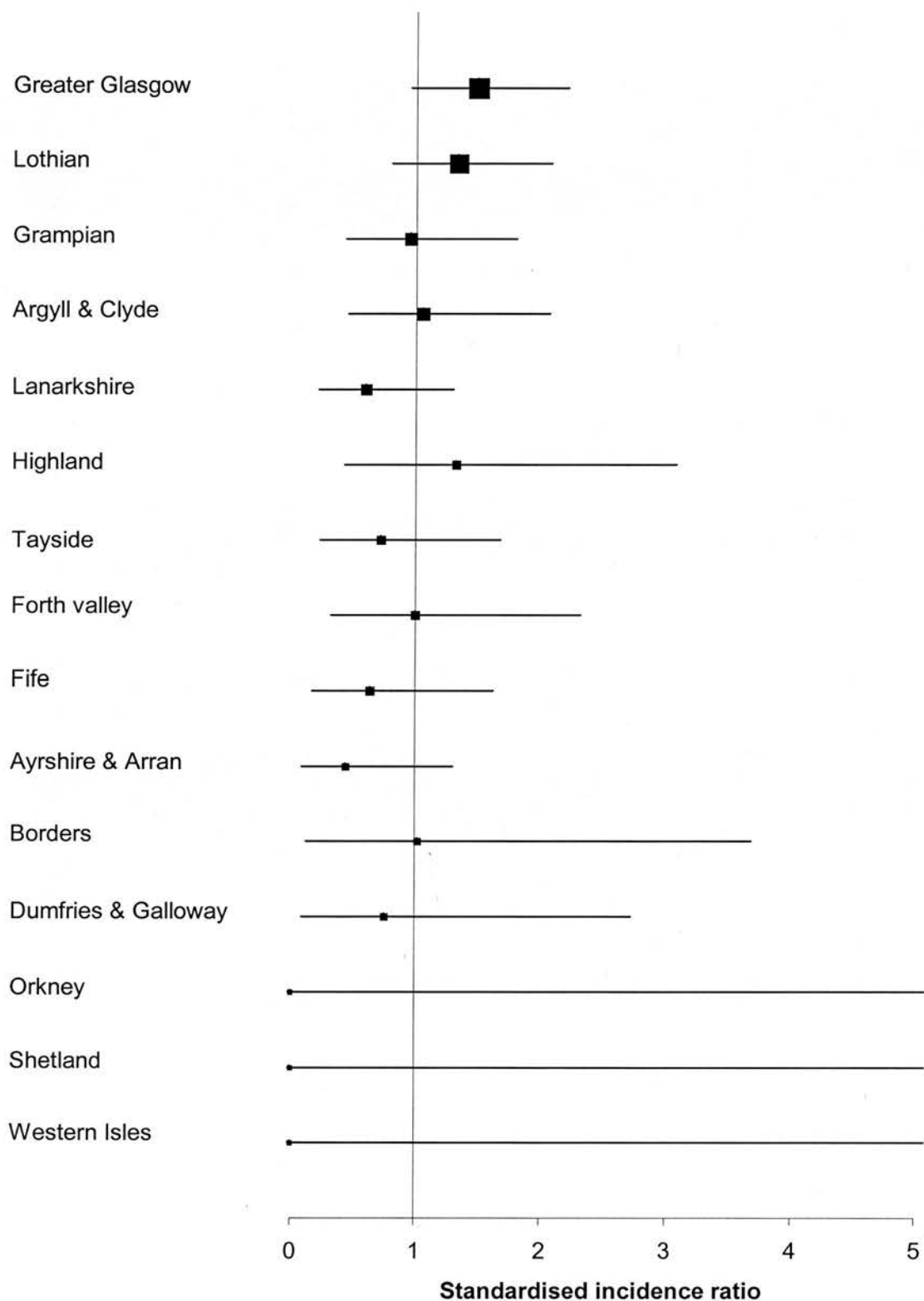
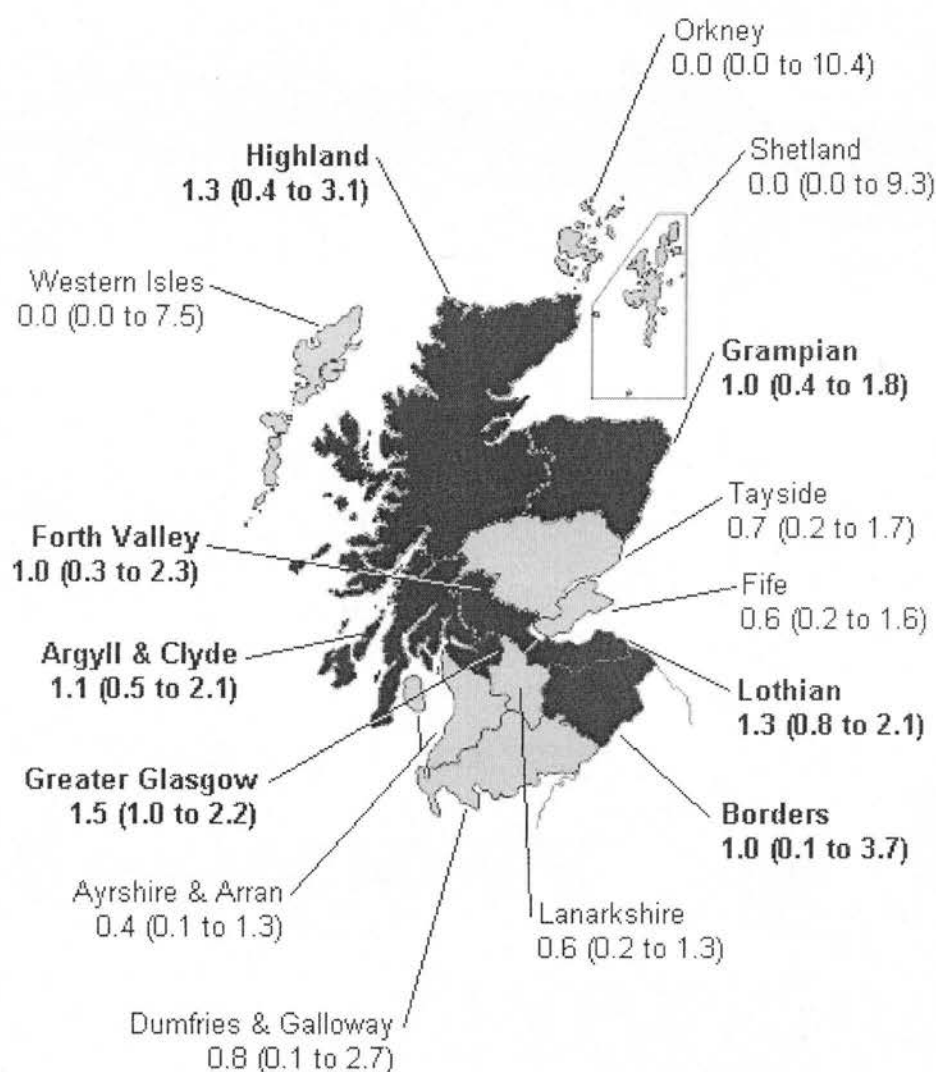


Figure 30 Age-standardised brain AVM incidence ratios for each of the 15 health boards in Scotland (bold if ratio ≥ 1)



**Chapter 9. The Scottish Intracranial Vascular Malformation Study
(SIVMS) – evaluation of ICD-10 coding and potential
sources of bias**

Chapter contents

- 9.1 Introduction
- 9.2 Utility of ICD-10 coding
 - 9.2.1 Sensitivity
 - 9.2.2 Positive predictive value
- 9.3 Evaluation of potential biases
 - 9.3.1 Simplified case ascertainment
 - 9.3.2 Pattern of diagnostic investigation
- 9.4 Summary
- 9.5 Discussion
 - 9.5.1 Utility of coding
 - 9.5.2 Bias in simplification of ascertainment

9.1 Introduction

In the previous chapter, I showed how routine coding of hospital discharge data and death certificates is an important source of ascertainment in SIVMS for the detection of cases occasionally missed by the collaborative network. Coding could, theoretically, be a single source of ascertainment in order to minimise the administrative and financial burden of maintaining the collaborative network. However, this would only be appropriate if coding were proven to be comprehensive and reliable. With this in mind, another research group has evaluated ICD-9 coding of brain AVMs at one hospital in New York, and found its specificity to be unacceptably poor [Berman *et al.* 2002]. This was unsurprising, since ICD-9 had only one code pertinent to IVMs (747.8, cerebrovascular anomaly). There has been no evaluation of the utility of ICD-10 coding of brain AVMs, which is likely to result in fewer false positives than ICD-9 because of its clear codes for brain AVMs (but sadly not other IVMs).

In this chapter I evaluate ICD-10 coding in order to provide data on the effectiveness of hospital coding departments in Scotland and collation of their output by ISD. To inform SIVMS's future methods of case ascertainment, I also evaluate a simulation of some potential biases. I pre-supposed that these could be introduced if inclusion in SIVMS were restricted to: routine coding as the sole means of case ascertainment, collaborators based at neuroscience centres as the sole means of case ascertainment, and using IADSA as the diagnostic standard for brain AVMs.

9.2 Utility of ICD-10 coding

I have evaluated the sensitivity and positive predictive value of the combination of the two ICD-10 codes for brain AVMs (Q28.2 and I60.8), by comparing the yield from coding in Scotland with overall case ascertainment to SIVMS, the latter regarded as the reference standard (Figure 31, page 203).

9.2.1 *Sensitivity*

The search of coding identified 58 (63%) of the 92 incident adults (Figure 27, page 191 and Figure 31, page 203). Of these 58 adults, coding contributed only four who were unknown to SIVMS because collaborators failed to notify us of them (Figure 31, page 203). To evaluate sensitivity, ISD used probability matching record linkage to detect records of any hospital admissions and/or death certificates of all 92 adults. Of the 34 adults missed by the search of coding, 11 would never have been detected because they had not died and were never hospital inpatients. This makes the 'true positive' denominator for the calculation of coding sensitivity 81 ([A-D] in Figure 31, page 203), resulting in a sensitivity of 72% (95%CI 61% to 80%). Coding missed the 'false negatives' [E] because of the incorrect allocation of Q27.3 to 8 adults and I67.1 to 3 adults (see Table 11, page 115); the remainder were due to brain AVM diagnoses not appearing on the discharge summary or death certificate, or missing records in the ISD dataset.

9.2.2 *Positive predictive value*

The search of coding for first-ever hospital admissions yielded 47 correctly coded but prevalent brain AVMs (because the adults had never been admitted to hospital in Scotland prior to the study period). Of the 67 adults with incorrectly allocated codes ('false positives'), intracranial aneurysms and perimesencephalic SAH accounted for the attribution of code I60.8, other IVM types were occasionally allocated the code Q28.2, and the diagnosis of a brain AVM was uncertain in 2 adults ([F] in Figure 31, page 203). The positive predictive value of an apparently incident code was 46% (95%CI 38% to 55%). Specificity cannot be calculated because the denominator for the calculation is impossible to quantify.

9.3 Evaluation of potential biases

9.3.1 *Simplified case ascertainment*

Only 58 (63%) of 92 adults would have been detected by coding alone, thereby underestimating the overall detection rate if coding was used as a single source of case ascertainment. Moreover, such a cohort would be biased towards younger people, with more haemorrhagic and fewer incidental presentations, greater investigation with IADSA and a strong tendency towards treatment (Table 16, page 202).

Furthermore, if SIVMS were to base its recruitment purely on collaborators at the four tertiary referral centres in Scotland (simulating a hospital-based cohort), it would have missed 8 (9%) of the 92 adults with a definite brain AVM. Comparing these eight adults with the other 84, fewer had had an IADSA (38% versus 77%, $\chi^2_{df=1}=6$, $p=0.014$) and fewer had been treated (13% versus 66%, $\chi^2_{df=1}=8.6$, $p=0.003$). The numbers were too small to detect any other disparities, but these differences reflect how specialist hospital cohorts are generally unrepresentative of the population at baseline, and are likely to remain so during follow-up.

9.3.2 *Pattern of diagnostic investigation*

Considering the reliance of other research groups on IADSA as the diagnostic reference standard, I was also interested in whether so doing would bias the SIVMS cohort.

In this population-based study, 68 (74%) of 92 adults with brain AVMs were investigated with IADSA, which led to definite diagnoses in 66 (72%) of them (Figure 32, page 204). The other 28% were diagnosed by CT, MRI or pathological examination. These investigation patterns resulted in a median time between clinical presentation and diagnosis for the 92 adults of 14 days (range 0 to 259 days), with delays reflecting the mode of presentation and occasional need for extensive and/or repeated investigation. Using IADSA as the diagnostic reference standard would have biased the cohort towards younger people (mean age 42 versus 56, two sample t-test $p=0.002$), more likely

to have presented with haemorrhage (52% versus 29%, Fisher's exact test, $p=0.011$), and to have been subsequently treated (77% versus 17%, $\chi^2_{df=1}=26.6$, $p=0.0000002$).

9.4 Summary

- Coding missed 37% of adults with brain AVMs, although it benefited SIVMS by being the sole source of 4% of the whole cohort of brain AVMs
- The sensitivity of ICD-10 coding of brain AVMs was 72% (95%CI 61% to 80%); false negatives were mainly due to incorrect coding, brain AVM diagnoses not appearing on the discharge summary or death certificate, or missing records in the coding dataset
- The positive predictive value of an apparently incident ICD-10 code for a brain AVM was 46% (95%CI 38% to 55%); false positives were mainly due to intracranial aneurysms and perimesencephalic subarachnoid haemorrhage (I60.8) and other IVM types (Q28.2)
- Even with as small a cohort as 92 adults, I have also been able to demonstrate that both simplified methods of case ascertainment and reliance on IADSA for diagnosis all would have biased the cohort, sometimes very seriously

9.5 Discussion

9.5.1 *Utility of coding*

The NHS has a long established coding infrastructure and the median accuracy of a wide variety of ICD codes in the UK has been found to be 84% [Campbell *et al.* 2001]. However, I knew from previous experience in Scotland that coding inaccuracies did make a large impact on the detection and mortality rates of motor neurone disease, a disease with a similar incidence to brain AVMs [Chancellor *et al.* 1993]. Regrettably, I

found the sensitivity and positive predictive value of ICD-10 coding of brain AVMs to be moderate in practice.

The utility of routinely collected data depends on the precision of diagnosis at death or at discharge from hospital. This is affected by the variable nomenclature used by clinicians, inadequate completion of the discharge summary and SMR01 form, as well as inaccuracies in transcription to ISD and its record linkage. 12% of adults with brain AVMs in SIVMS were not admitted to hospital in the year of their diagnosis. Coding might only identify these people some time after inception, depending on whether they die and whether they are admitted for further investigation or treatment.

Moreover, the adequacy of ICD coding depends on the existence of relevant codes. ICD-9 used a single code (747.8) for ‘cerebrovascular anomalies’ – encompassing a heterogeneous spectrum of IVMs and other lesions – which has been shown to have a 94% (95%CI 91% to 96%) sensitivity but poor specificity in one New York hospital [Berman *et al.* 2002]. The transition to ICD-10 has merely created an explicit code for brain AVMs, but not for the other IVMs. In doing so, ICD-10 appears to have diminished the sensitivity of coding for brain AVMs (although direct comparison with the New York study is not possible, because they evaluated all IVMs, and not just brain AVMs). This is unsurprising, because coders need time and training to become familiar with a new coding scheme; furthermore, the continued existence of categories bearing descriptions such as, ‘other...’ and, ‘not otherwise specified...’ will result in those less familiar with the dedicated codes allocating non-specific catch-all codes to brain AVMs.

9.5.2 *Bias in simplification of ascertainment*

The administrative burden of maintaining a collaborative network and following people prospectively through their medical records questions whether coding alone would be a satisfactory means of ascertaining and following-up incident adults. Sadly, I have found that adults who are coded are a biased group. Using coding for follow-up would also subject this group to the accuracy of record linkage and coding of death certificates, and it would miss any important outcomes (such as epilepsy) not resulting in hospital admission. Furthermore, restricting the collaborative network to those based at neuroscience centres (implying a special interest in brain diseases) would further bias the

cohort towards patients identified by the investigation practices of specialists, missing patients detected at district hospitals who are not referred onwards. This may be due to the still scarce provision of neurologists in the UK or perhaps due to characteristics of the patients themselves.

This exploration of ICD-10 coding, and the potential biases introduced by an otherwise attractive simplification of SIVMS's methods of ascertainment, reinforces the need for SIVMS to continue using its current design. Furthermore, inclusion criteria encompassing diagnoses that can be made using non-invasive imaging alone do result in a less biased cohort. Because IADSA is available for 74% of the cohort, SIVMS will only be able to explore variants of angioarchitecture as prognostic factors in this proportion. But before describing angioarchitecture and exploring its influence on prognosis, it is important to quantify the degree of observer variation in its determination, which I do in the next chapter.

Table 16 Comparisons of the demographic and clinical details of subsets of adults incident with a definite brain AVM in 1999 and 2000, according to whether they were detected by coding or not

Characteristic	SIVMS (n=92)	Coded (n=58)	Not coded (n=34)	Test *	Significance
Age at presentation (mean \pm SD)	45 \pm 16	42 \pm 12	52 \pm 19	Two sample t-test (t=-2.8)	p=0.007
Male (%; 95%CI)	53 (43 to 63)	59 (46 to 70)	44 (29 to 61)	$\chi^2_{df=1} = 1.8$	p=0.178
Mode of presentation					
haemorrhage (%; 95%CI)	46 (36 to 56)	57 (44 to 69)	26 (15 to 43)	Fisher's exact test [§]	p=0.004
epilepsy (%; 95%CI)	26 (18 to 36)	28 (18 to 40)	27 (15 to 43)		
incidental (%; 95%CI)	21 (14 to 30)	10 (5 to 21)	38 (24 to 55)		
other (%; 95%CI)	7 (3 to 14)	5 (2 to 14)	9 (3 to 23)		
Presence of aneurysm(s) (%; 95%CI)	22 (15 to 31)	22 (14 to 35)	21 (10 to 37)	$\chi^2_{df=1} = 0.04$	p=0.838
Catheter angiography (%; 95%CI)	74 (64 to 82)	90 (79 to 95)	47 (32 to 63)	$\chi^2_{df=1} = 20.2$	p=0.000007
Treated with embolisation, excision, or radiotherapy (%; 95%CI)	61 (51 to 70)	76 (64 to 85)	35 (22 to 52)	$\chi^2_{df=1} = 14.8$	p=0.0001

* Tests of statistical significance compared adults who were coded with those who were not

[§] Significance was tested across all four modes of presentation in a 4x2 table

Figure 31 Comparison of ascertainment by the disease register with coding of hospital discharge and death certificate data

Utility of ICD-10 codes Q28.2 and I60.8 for identifying adults with a definite brain AVM:

Sensitivity = $[B + C] / [A - D]$

Positive predictive value = $[B + C] / [B + C + F]$

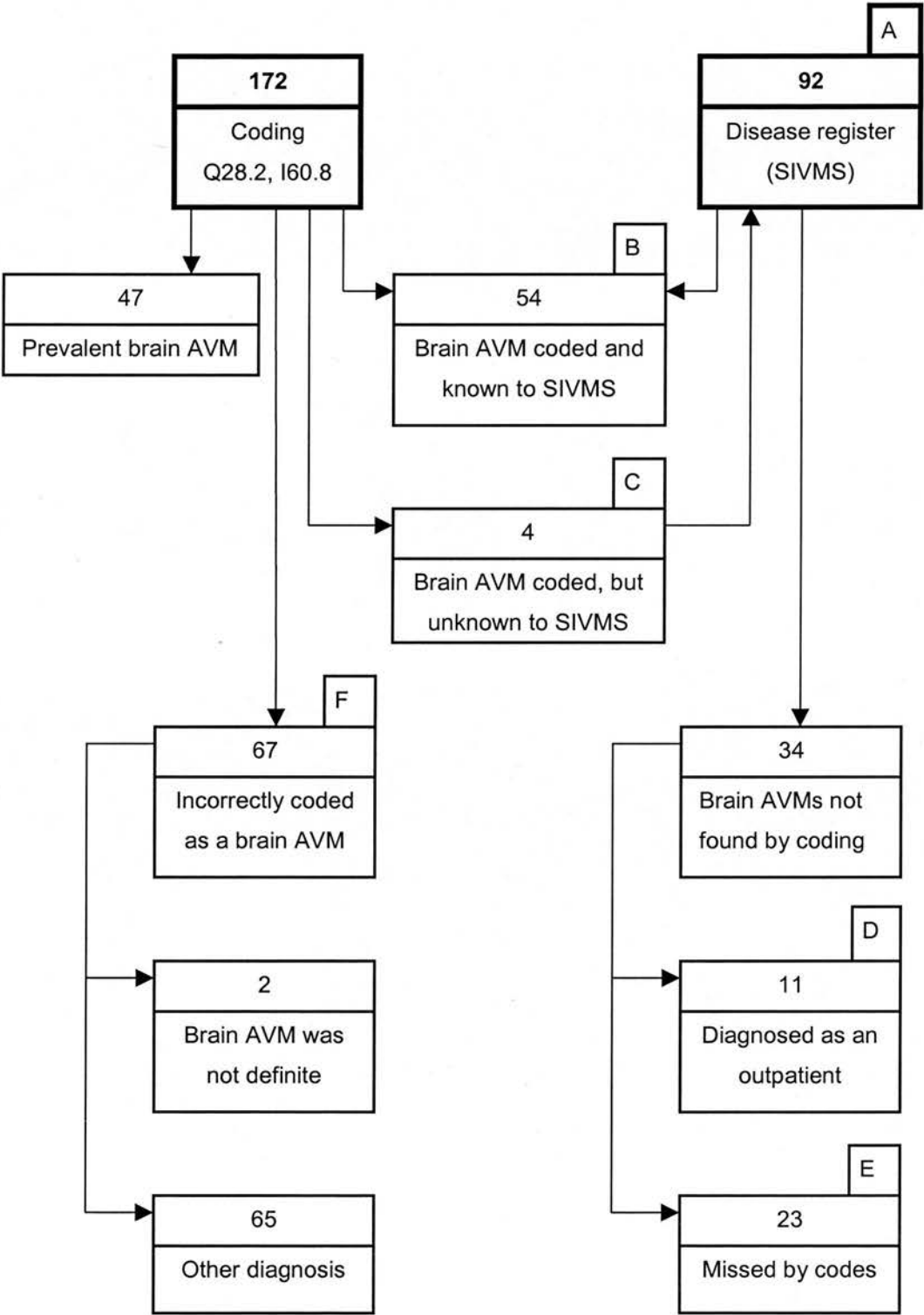
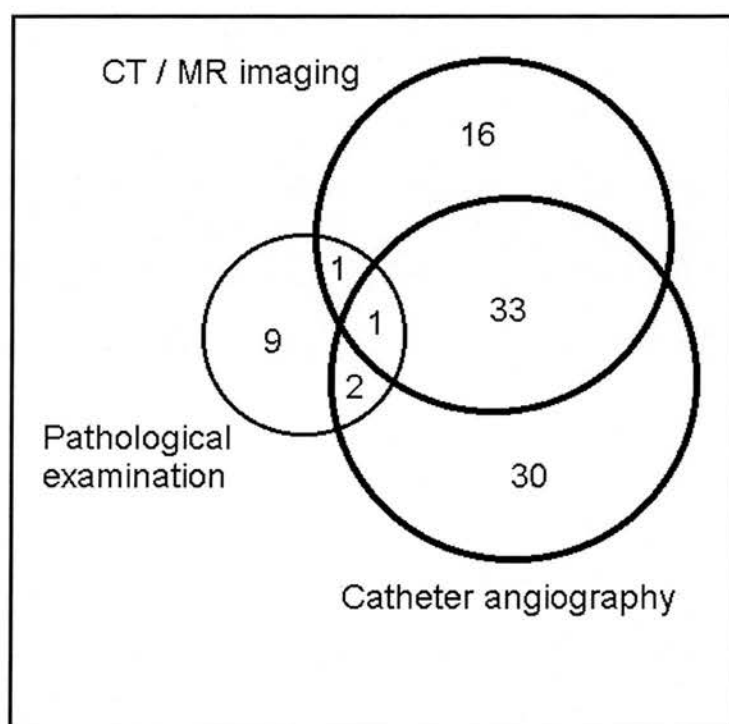


Figure 32 Investigations that led to a definite diagnosis of a brain AVM for the 92 incident participants

Pathological examination = autopsy or specimen from surgical excision



Chapter 10. Observer variation in the interpretation of catheter angiograms of brain AVMs

Chapter contents

- 10.1 Introduction
- 10.2 Methods
 - 10.2.1 Angiograms
 - 10.2.2 Observers
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 - 10.2.5 Data processing
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- 10.4 Summary
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 - 10.5.1.2 Precision
 - 10.5.1.3 Kappa caveats
 - 10.5.2 Implications for routine practice
 - 10.5.2.1 Evaluate nidus size with standardised calibration markers
 - 10.5.2.2 Perform angiography which is adequate to characterise subtle angioarchitecture
 - 10.5.3 Future research

10.1 Introduction

The angioarchitecture of brain AVMs demonstrated on IADSA is thought to influence their prognosis [Al-Shahi and Warlow 2001], and is therefore often used to decide whether and how to treat a brain AVM [Nataf *et al.* 1998; Mansmann *et al.* 2000]. However, accurate description of angioarchitecture is inevitably affected by the inherent complexity of AVMs, the extent and quality of their imaging, neuroradiologists' personal interpretations of it, and human error. These sources of observer variation are likely to have been compounded by inconsistencies in angioarchitecture terminology used in the literature, varying perceptions of what is abnormal, and – until very recently – the lack of structured definitions intended for widespread use [Joint Writing Group 2001].

Previously, there has been just an abstract reporting agreement about AVM size and morphology using World Wide Web based joint photographic expert group (JPEG) format magnetic resonance and angiographic images [Stapf *et al.* 2000a]. This study's response rate was 63%, only 2 of 19 participants were neuroradiologists, and JPEG images rather than hard copies of IADSAs were used.

Because I anticipated that inter-observer variation could complicate the data collection process for SIVMS, the two study neuroradiologists have reviewed every diagnostic IADSA together. In the meantime, I took the opportunity to use the IADSA studies collected by SIVMS to evaluate inter- and intra-observer variation, necessarily having to involve observers outside Scotland because of their unfamiliarity with the study patients.

10.2 Methods

10.2.1 Angiograms

In order to be representative of everyday practice, I used the IADSA studies of 40 patients – obtained at the time of first-ever brain AVM diagnosis – from the first year of SIVMS. I used identical copies of the entire run of the four-vessel IADSA that made the first-ever brain AVM diagnosis. The IADSAs were performed at the four neuroscience centres in Scotland; they included all the antero-posterior, lateral and oblique views and

vascular territories necessary to visualise the brain AVM, and only omitted normal vascular territories and frames from superselective vascular catheterisation performed prior to embolisation. Because of the different facilities for angiography, the spectrum of experience of the radiologists in Scotland, and the variable resolution of copy films, the 40 IADSAs inevitably varied in quality. In order to explore the influence of film quality, the two non-participating SIVMS neuroradiologists rated the quality of the films prior to starting the study (12 were 'excellent', 18 were 'good', 8 were 'average', 2 were 'poor' but none was 'terrible'). Axial CT or MRI from the presentation that led to diagnosis was included to aid localisation. Size markers on CT and MRI were obscured to force observers to estimate nidus dimensions from the IADSA.

10.2.2 Observers

The 5 observers were practising consultant interventional neuroradiologists in the UK (Table 17, page 218). They worked in separate cities and had never been involved in the management of any of the patients in SIVMS. They interpreted IADSAs without knowledge of clinical details, the original imaging findings or each other's results. The observers were not presented with definitions of any of the angioarchitectural features under investigation, and – as often occurs in everyday practice – they used the diameter of the genu of the petrous portion of the internal carotid artery (5mm) as a reference for sizing a nidus, either using callipers or a customised scale on paper [Paullus *et al.* 1977].

10.2.3 Angiogram distribution

The 40 IADSAs were distributed and reviewed in two batches between January and May 2001. Every IADSA was reviewed by 2 of the 5 observers for the inter-observer study, and 38 of the 40 IADSAs were reviewed by the same observer on two separate occasions for the intra-observer study. The IADSAs were divided amongst the observers so that each neuroradiologist was allocated a similar spectrum of brain AVMs according to crude indicators of their nidus diameter (2 large ($>6\text{cm}$), 14 medium, 24 small ($<3\text{cm}$)) and vascular complexity (18 simple (≤ 2 feeders or draining veins) and 22 complex (>3 feeders or draining veins)).

10.2.4 Data collection

A standard data collection form was distributed with each IADSA to collect the following data:

Data collected (forced categories are described in brackets)

- Depth (deep, superficial)
 - Nidus diameter (mm) in 3 dimensions (antero-posterior, transverse and vertical)
 - Number of feeding arteries
 - Feeding artery angiopathy (yes, no), and if present whether abnormally dilated, stenosed, or both dilated and stenosed [Pile-Spellman *et al.* 1986]
 - Angiogenesis (yes, no) [Mansmann *et al.* 2000]
 - Collateral supply (yes, no), and if present whether dural, pial/leptomeningeal, or both dural and leptomeningeal [Russell and Berenstein 1981]
 - Nidus border (compact/diffuse) [Chin *et al.* 1992]
 - Discernible fistula in the nidus (yes, no) [Houdart *et al.* 1993]
 - Number of draining veins/nidus compartments [Albert *et al.* 1990]
 - Spetzler-Martin surgical grade
calculated by an observer summing scores from the scale provided for AVM nidus size, pattern of venous drainage and eloquence of adjacent brain (although constituent scores on each of these 3 items were not collected) [Spetzler and Martin 1986]
 - Venous varices (yes, no) [Lasjaunias *et al.* 1986]
 - Venous ectasia (yes, no) [Lasjaunias *et al.* 1986]
 - Venous stenosis (yes, no) [Viñuela *et al.* 1985]
 - Aneurysm(s) (yes, no), and aneurysm type if identified (feeding artery, nidal, pseudo-aneurysm [Garcia-Monaco *et al.* 1993], remote) [Redekop *et al.* 1998]
-

10.2.5 *Data processing*

All data were double-punched to ensure accuracy of data entry. Because the same observer reviewed some IADSA on two separate occasions for the intra-observer agreement study, only data from the earliest date that an observer reviewed a particular IADSA were used to evaluate inter-observer agreement.

10.2.6 *Statistical analysis*

The primary outcomes in this study were observer variation quantified by the kappa statistic (κ) for nominal data (e.g. dichotomous yes/no answers) [Cohen 1960], the weighted κ statistic for ranked ordinal data (e.g. Spetzler-Martin grade) and discrete interval data (e.g. number of feeders) [Cohen 1968], and Bland & Altman analysis for continuous data (e.g. nidus dimensions in millimetres) [Bland and Altman 1986; Rothwell 2000]. Percentage agreement between observers is not a good measure, because – unlike κ (Figure 33, page 220) – it does not discriminate between actual agreement and agreement which arises due to chance.

The raw data were re-coded for some variables to enable a simple assessment of observer agreement using the κ statistic, although I did also examine cross tabulations of the raw data and Bland & Altman plots for these variables where appropriate (e.g. nidus dimensions, Figure 35, page 222). For example, nidus size in each of the three dimensions was re-coded into a dichotomous variable according to whether an observer found them to be $\geq 30\text{mm}$ or $< 30\text{mm}$ (the size threshold for stereotactic radiosurgery). The numbers of feeding arteries and draining veins were re-coded as 1, 2, or ≥ 3 because different radiologists had different thresholds for deeming there to be ‘multiple’ vessels when they were too numerous to count, which made Bland & Altman analysis of these variables impossible.

All analyses were performed in Statistical Product for the Social Sciences (SPSS) version 10.0.5 except confidence intervals for κ , which were calculated using Confidence Interval Analysis software [Altman *et al.* 2000], and weighted κ tests and their confidence intervals, which were calculated in Statistical Analysis Software (SAS) version 8.

10.2.7 Sample size calculation

The study was designed with 87% power to detect a greater than fair agreement ($\kappa=0.4$) at the $p=0.05$ level of significance, assuming the level of agreement for the characteristics would be substantial ($\kappa=0.7$) [Walter *et al.* 1998].

10.3 Results

Complete responses were received from all 5 observers, and the median time between an observer reporting the two batches of IADSAs for the intra-observer study was 5 (range 4 to 6) months. The interpretation of inter-observer agreement requires a prior appreciation of intra-observer agreement because between-observer variation is inevitably affected by the extent of within-observer variation.

Figure 34 (page 221) demonstrates that for every characteristic intra-observer agreement was greater than inter-observer agreement. Intra-observer agreement was mostly moderate to substantial with 95% confidence intervals ranging from fair to almost perfect. Inter-observer agreement was mostly slight to moderate, with 95% confidence intervals ranging from less than chance to almost perfect.

Intra-observer agreement about whether the diameter of an AVM nidus was $\geq 30\text{mm}$ or $< 30\text{mm}$ ranged from substantial to almost perfect, whereas inter-observer agreement was somewhat worse. Plotting the raw, continuous nidus size data on Bland & Altman plots reveals a tendency for both intra- and inter-observer variation to increase as nidus size increases, especially above 20mm. Using the transverse nidus dimension as an example (Figure 35, page 222), the greater scatter about the mean for inter-observer as opposed to intra-observer comparisons of raw continuous data explains why $\kappa=0.36$ for inter-observer comparisons as opposed to $\kappa=0.78$ for intra-observer comparisons using categorical data with a 30mm size threshold (Figure 34, page 221).

Inter-observer agreement was greatest for characteristics such as determining whether nidus diameter was $\geq 30\text{mm}$ or $< 30\text{mm}$ (e.g. vertical dimension $\kappa = 0.62$ (95%CI 0.37 to 0.88)), and whether there were venous varices or not ($\kappa = 0.56$ (95%CI 0.31 to 0.81)). In general there was the greatest overall agreement between observers for AVMs with

simple angioarchitecture lacking many of the features of interest (Figure 36, page 223). Inter-observer agreement was worst for characteristics such as venous stenosis ($\kappa = 0.14$ (95%CI -0.33 to 0.60)), angiogenesis ($\kappa = 0.18$ (95%CI -0.13 to 0.49)), and the type of nidus border ($\kappa = 0.22$ (95%CI -0.20 to 0.64)) – in other words, AVMs with more complex angioarchitecture (Figure 36, page 223). Alarming, inter-observer agreement was only moderate for the variables with the greatest importance in routine practice: Spetzler-Martin grade, which influences predictions of morbidity from surgery (weighted $\kappa = 0.47$ (95%CI 0.30 to 0.64)), and the presence of aneurysms, which are thought to confer a greater risk of subsequent haemorrhage and may also influence management decisions ($\kappa = 0.40$ (95%CI 0.11 to 0.68)).

I asked observers to assess IADSA quality with the intention of exploring whether it influenced observer agreement. However, intra-observer agreement about IADSA quality was $\kappa = 0.43$ (95%CI 0.20 to 0.67), and inter-observer agreement was $\kappa = 0.19$ (95%CI -0.04 to 0.42), making stratification of kappas by quality for each angioarchitectural feature susceptible to observer variation in the determination of quality. Moreover, the small number of observations in each quality category resulted in even wider confidence intervals around the kappa estimates, and I found no consistent trend towards a better level of agreement for higher quality films.

10.4 Summary

- This study of 5 neuroradiologists' interpretations of 40 IADSA studies was a pragmatic effort to understand both intra- and inter-observer agreement in day-to-day assessment of AVM angioarchitecture
- The IADSAs were of adequate quality, although it will always be difficult to reflect the dynamic nature of angiography in hard copy format
- Unsurprisingly, there was greater intra-observer than inter-observer agreement
- Inter-observer agreement was greatest for characteristics such as nidus size (although there was a tendency for variation to increase as nidus size increases), moderate for Spetzler-Martin grade and the presence of

aneurysms, and worst for the presence of venous stenosis and type of nidus border

10.5 Discussion

The findings of this study should be regarded as a baseline measure of observer agreement for future studies, the results should be considered in the light of important statistical caveats common to all studies using κ , and they have some implications for routine practice.

10.5.1 *Statistical considerations*

10.5.1.1 Bias, confounding and chance

I avoided bias by using IADSA that the study neuroradiologists had never seen before, by anonymizing films, and by leaving a median of 5 months between an observer re-reviewing the same IADSA (to lessen recognition effects). By distributing IADSA evenly according to image quality and AVM complexity, I sought to minimise confounding. Chance effects were minimised by ensuring the study was adequately powered to detect a difference from only fair agreement ($\kappa = 0.4$), assuming agreement would be substantial ($\kappa = 0.7$) for any characteristic. Indeed I confirmed my suspicion that intra-observer agreement was of this order for most angioarchitectural features (Figure 34, page 221).

10.5.1.2 Precision

To establish the extent of observer agreement with greater precision, a larger study will be required. This could be achieved by increasing the number of observers and/or IADSA, which would also enable an analysis of the bias of any individual observer (10.5.3, page 216). A greater number of IADSA for which there are two observer comparisons would certainly narrow the 95% confidence intervals around estimates of κ

(Figure 34, page 221), but having more than two observers per IADSA would complicate the statistical analysis.

10.5.1.3 Kappa caveats

Although there are several well-rehearsed caveats to the use of κ [Brennan and Silman 1992], and experts debate whether or not the intraclass correlation coefficient is a better measure [Maclure and Willett 1987], κ is nevertheless the most frequently used index of agreement. κ relies on both the subjects under study and the observers being independent, and that the categories in the scale are independent, mutually exclusive and exhaustive [Cohen 1960]. These assumptions held for this study, although varying beliefs about angioarchitecture between research groups (a form of global observer variation) will affect whether readers perceive overlap between categories for some characteristics.

The greater the number of scale categories, the lower κ will inevitably be, so agreement will tend to appear better with a dichotomous scale [Brennan and Silman 1992]. For example, κ for inter-observer agreement falls from 0.29 to 0.19 when subdividing angiopathy into more than yes/no categories and it falls from 0.41 to 0.30 when subdividing collateral supply into more than yes/no categories). Conversely, using only 3 categories for the numbers of feeding and draining vessels masked variation; I would have used Bland & Altman analysis were it not for different thresholds between observers for declaring vessels “multiple”.

An artefact of κ is that it is affected in complex ways by both the prevalence of abnormality amongst the subjects used and also by observer bias [Brennan and Silman 1992; Byrt *et al.* 1993]. Firstly, most characteristics in this study were unevenly distributed between their different sub-categories (the most extreme being venous stenosis and nidus border), although the distribution of some features such as aneurysms was more even (Table 18, page 219). The nature of my sample means this probably reflects the population distribution of these abnormalities. But when marginal totals are unbalanced, or expected levels of agreement are high because of a high underlying prevalence, κ is fragile and examination of the influences of prevalence effects will be essential when comparing studies [Byrt *et al.* 1993]. Secondly, agreement is

only one aspect of variation between observers, the other being biases between them (e.g. a tendency for one observer to systematically overestimate nidus size) [Brennan and Silman 1992]. I avoided this sort of bias by ensuring each neuroradiologist was observer 1 or observer 2 a comparable number of times in the inter-observer study, and each neuroradiologist was equally represented in the intra-observer study.

When there are several ordinal scale categories (e.g. Spetzler-Martin grade), between which large disagreements are more serious but would be treated as equally serious by κ , the weighted κ can be used when the relative seriousness of disagreements is specified [Cohen 1968]. In this study I allocated weights evenly (e.g. weights of 1, 0.75, 0.5, 0.25 and 0 for Spetzler-Martin grades 1 to 5), but whether and how uneven weighting should be used to reflect clinically important thresholds (such as ≤ 2 and ≥ 3 on the Spetzler-Martin scale) is debatable.

10.5.2 *Implications for routine practice*

The high level of intra-observer agreement shows that experienced interventional neuroradiologists are consistent, but poor inter-observer agreement shows that assessment and interpretation differ between them. This argues for caution in interpreting prognosis and basing treatment decisions on angioarchitectural features with less than adequate inter-observer agreement.

10.5.2.1 Evaluate nidus size with standardised calibration markers

There are several barriers to accurately sizing an AVM on an IADSA, which are reflected by the scatter of size estimates in Figure 35 (page 222). The definition of a nidus as the area towards which multiple feeding arteries converge and from which enlarged veins drain is somewhat arbitrary [Doppman 1971]. This is especially problematic when nidus morphology is diffuse (Figure 18A-C, page 166) [Chin *et al.* 1992], and when the AVM is a simple fistula (Figure 36, page 223, which elicited nidus dimensions of 0-20mm in this study). The nidus is often not imaged in its entirety when catheterising single vascular territories during IADSA, making the maximum linear diameter in any dimension difficult to gauge [Soderman *et al.* 2000]. It is therefore hard

to imagine how proposed nidus volume calculations [Pasqualin *et al.* 1991; Soderman *et al.* 2000], dependent on further assumptions about the shape of the nidus, can be accurate. Moreover, magnification or minification by both film projection and digital subtraction imaging distorts the abnormal vessels. Without reference markers, the widespread use of the diameter of the genu of the petrous portion of the internal carotid artery – as in this study – can be inaccurate; for example, it is larger than 5mm if feeding ipsilateral, large, high-flow brain AVMs. Potential solutions to these sources of measurement error include consistent angiographic magnification factors, widespread use of simple calibration markers such as rulers, washers and coins (which were not in frequent use a decade ago [Soderman *et al.* 2000], and do not seem to be now), and magnification/minification rulers [Forbes *et al.* 1996]. The routine use of standardised calibration markers on IADSA is therefore essential to reduce variation in which patients are considered – and then further evaluated with stereotactic sizing [Elisevich *et al.* 1995] – for stereotactic radiosurgery. Given the many sources of error in assessing nidus size on IADSA, perhaps MRI should be used in preference, as has been SIVMS's policy. I will compare measurements of nidus size using different types of imaging later (14.3.2, page 275).

10.5.2.2 Perform angiography which is adequate to characterise subtle angioarchitecture

The reliable characterisation of angioarchitectural features of interest usually requires imaging of suspected abnormalities in at least two planes (e.g. identification of aneurysms and venous stenosis) [Joint Writing Group 2001]. This should be the required standard of routine clinical practice. Super-selective angiography further assists expert neuroradiologists in their interpretation of arterial supply (e.g. the number of feeders) and the nidus (e.g. whether there is a single fistula within it). But the balance between the risks and benefits of the routine use of super-selective angiography has not been established, and there are no data on whether it carries greater risks than routine IADSA.

10.5.3 *Future research*

The results of this study argue that the further development of acceptable radiological definitions and future studies of observer agreement should be prioritised in certain areas.

Agreement about nidus size should be re-evaluated on MRI and when standardised angiographic calibration markers are in widespread use, because of the importance of size in determining who is eligible for stereotactic radiosurgery.

The Spetzler-Martin grading system is in widespread use to predict morbidity from surgical excision, but the observed levels of intra-observer (weighted $\kappa = 0.63$ (95%CI 0.48 to 0.79)) and inter-observer (weighted $\kappa = 0.47$ (95%CI 0.30 to 0.64)) agreement are cause for some concern. In addition to nidus size, the other two components of the Spetzler-Martin grading system (eloquence of adjacent brain and pattern of venous drainage) should be explored. It will be interesting to discover which of the three components is most responsible for less than perfect observer agreement in the use of this scale. In this study, observers assumed left hemisphere dominance for the determination of eloquence. To assist with determination of eloquence, future studies might benefit from a brief clinical history accompanying each IADSA. However, this benefit might be offset by indirectly encouraging over-interpretation of some angioarchitectural features in cases with a more severe presentation, thereby introducing bias.

Since a worse prognosis for the first occurrence of haemorrhage seems to be conferred by the identification of aneurysms in conjunction with unruptured AVMs [Al-Shahi and Warlow 2001] (especially those in the nidus, not thought to be pseudoaneurysms [Elisevich *et al.* 1995]), efforts should be made to understand why inter-observer agreement about the very presence of aneurysms was only $\kappa=0.40$ (95%CI 0.11 to 0.68). This is likely to be only partly explained by neuroradiologists in this study reviewing hard copies of the IADSAs, rather than performing them, and superselective studies not being available. It will be important to further evaluate agreement about the presence of aneurysms (distinct from infundibula), their number, their locations and whether or not they should be treated.

In this study individual observers' thresholds for declaring feeding or draining vessels multiple appeared to differ. Clearly, the ability to correctly define feeding vessel anatomy is to some extent dependent on the use of superselective angiography – neuroradiologists do occasionally discover unsuspected feeders only at the time of embolisation. Therefore, the only way for me to interpret agreement about feeding and draining vessel anatomy was to group the raw, continuous data about numbers of vessels into three simple ordinal categories (1, 2, or ≥ 3 vessels), although some authors have reservations about this statistical approach [Maclure and Willett 1987]. Whilst there are no clear data about the absolute number of feeding or draining vessels carrying particular prognostic importance, future studies might profit from assessing the agreement about the original vascular territories of feeding vessels, because this too may determine outcome [Stapf *et al.* 2000b].

Particular emphasis should be placed on developing internationally agreed definitions for the characteristics above [Joint Writing Group 2001], and for those features which had the greatest inter-observer variation in this study (angiopathy, angiogenesis, collateral supply, nidus border, discernible fistula and venous stenosis). Thereafter, using this study as a baseline measure of observer agreement prior to publication of the Joint Writing Group's definitions [Joint Writing Group 2001], it will be important to reassess observer agreement in larger studies, amongst neuroradiologists from different countries, and using emerging techniques (such as MR and digital angiography, image manipulation and reconstruction).

From the point of view of SIVMS, the data in this study are of interest in as much as they refer to observer agreement amongst interventional neuroradiologists of comparable experience to the two study neuroradiologists. In future, I would like to explore the observer variation between the two SIVMS neuroradiologists, but this will require an IADSA set from another research group.

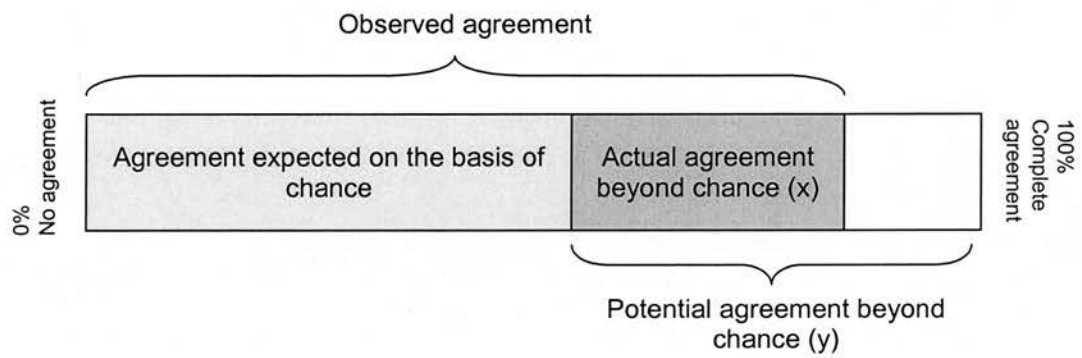
Table 17 Characteristics of the 5 observers (all consultant interventional neuroradiologists)

Observer	Length of practice as a consultant specialist (years)	Special interest in AVMs?	AVM interventional procedures performed (per year)
A	10	Yes	15-30
B	12	Yes	40
C	8	Yes	6
D	7	Yes	15
E	21	Yes	30

Table 18 Percentage agreement about the different variables in the intra-observer and inter-observer agreement studies

% disagreement = $100 - \Sigma(\text{prevalence of agreement in each category})$

Variable	% prevalence of agreement (intra-observer study)	% prevalence of agreement (inter-observer study)
AVM depth		
▪ Deep	24	23
▪ Superficial	58	53
Anteroposterior diameter		
▪ $\geq 3\text{cm}$	34	23
▪ $< 3\text{cm}$	55	58
Transverse diameter		
▪ $\geq 3\text{cm}$	34	23
▪ $< 3\text{cm}$	55	48
Vertical diameter		
▪ $\geq 3\text{cm}$	37	28
▪ $< 3\text{cm}$	53	55
Number of feeders		
▪ 1	16	5
▪ 2	13	10
▪ ≥ 3	45	45
Angiopathy		
▪ Yes	50	40
▪ No	26	15
Angiogenesis		
▪ Yes	32	18
▪ No	58	43
Collateral supply		
▪ Yes	29	23
▪ No	58	50
Nidus border		
▪ Compact	68	68
▪ Diffuse	18	8
Discernible fistula		
▪ Yes	29	20
▪ No	58	48
Number of veins		
▪ 1	32	33
▪ 2	11	5
▪ ≥ 3	34	28
Spetzler-Martin grade		
▪ 1	13	10
▪ 2	11	18
▪ 3	16	5
▪ 4	16	8
▪ 5	3	3
Venous varices		
▪ Yes	37	30
▪ No	55	48
Venous ectasia		
▪ Yes	55	55
▪ No	24	18
Venous stenosis		
▪ Yes	13	5
▪ No	74	70
Aneurysms		
▪ Yes	29	30
▪ No	58	40

Figure 33 The kappa statistic [Cohen 1960]

$$\text{Kappa } (\kappa) = \frac{\text{Actual agreement beyond chance (x)}}{\text{Potential agreement beyond chance (y)}}$$

Figure 34 The extent of intra-observer (open boxes) and inter-observer (filled boxes) agreement, measured by the un-weighted or weighted (asterisked) κ , shown as point estimates with 95% confidence intervals
Qualitative ranges for the extent of agreement measured by κ are marked with dotted lines (0.8-1 almost perfect; 0.6-0.8 substantial; 0.4-0.6 moderate; 0.2-0.4 fair; 0-0.2 slight; <0 agree less than chance)

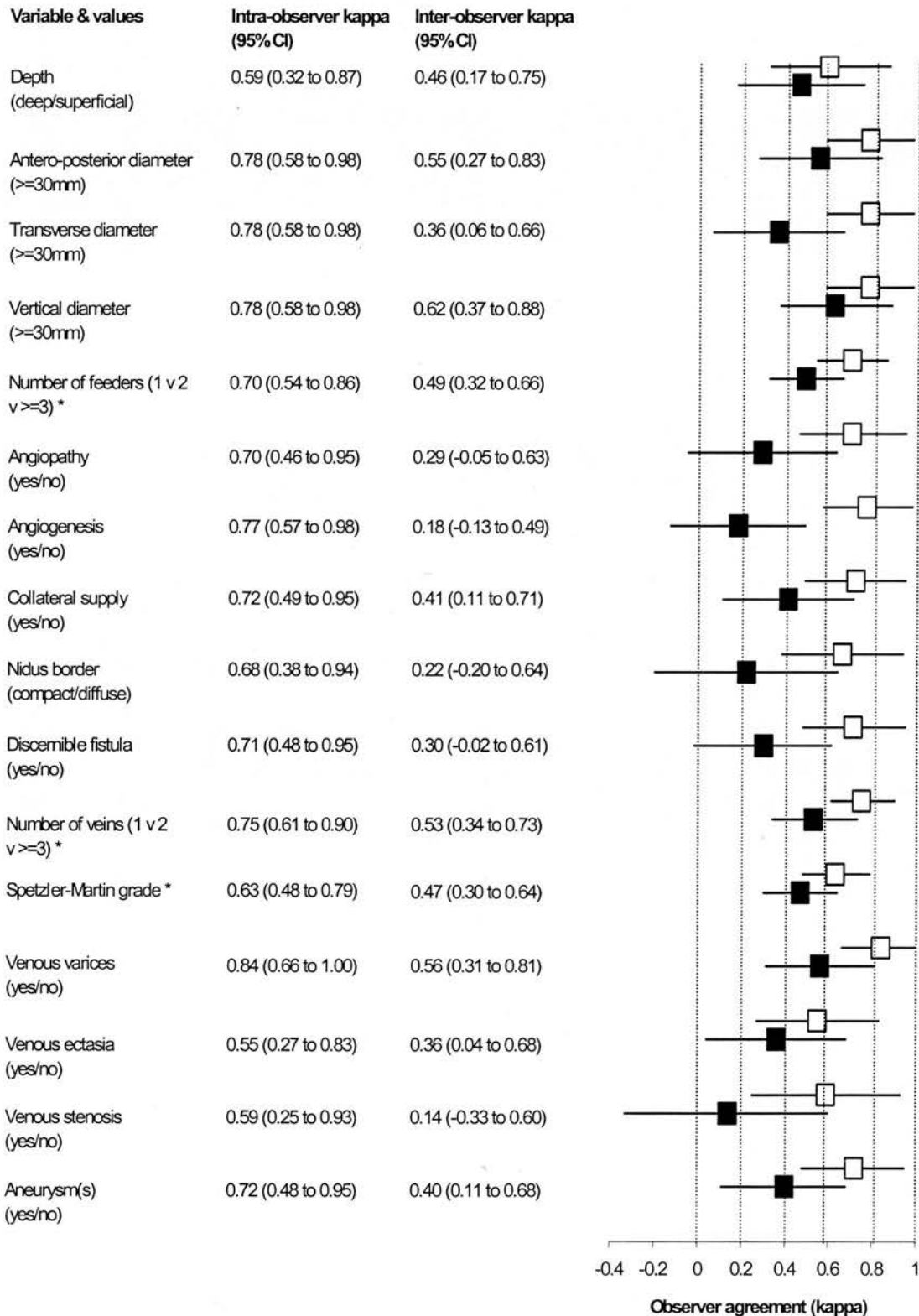


Figure 35 Bland & Altman plots of the difference between paired observations of nidus size in the transverse dimension (mm) against the mean of the observations (mm) for intra-observer (above) and inter-observer comparisons (below)

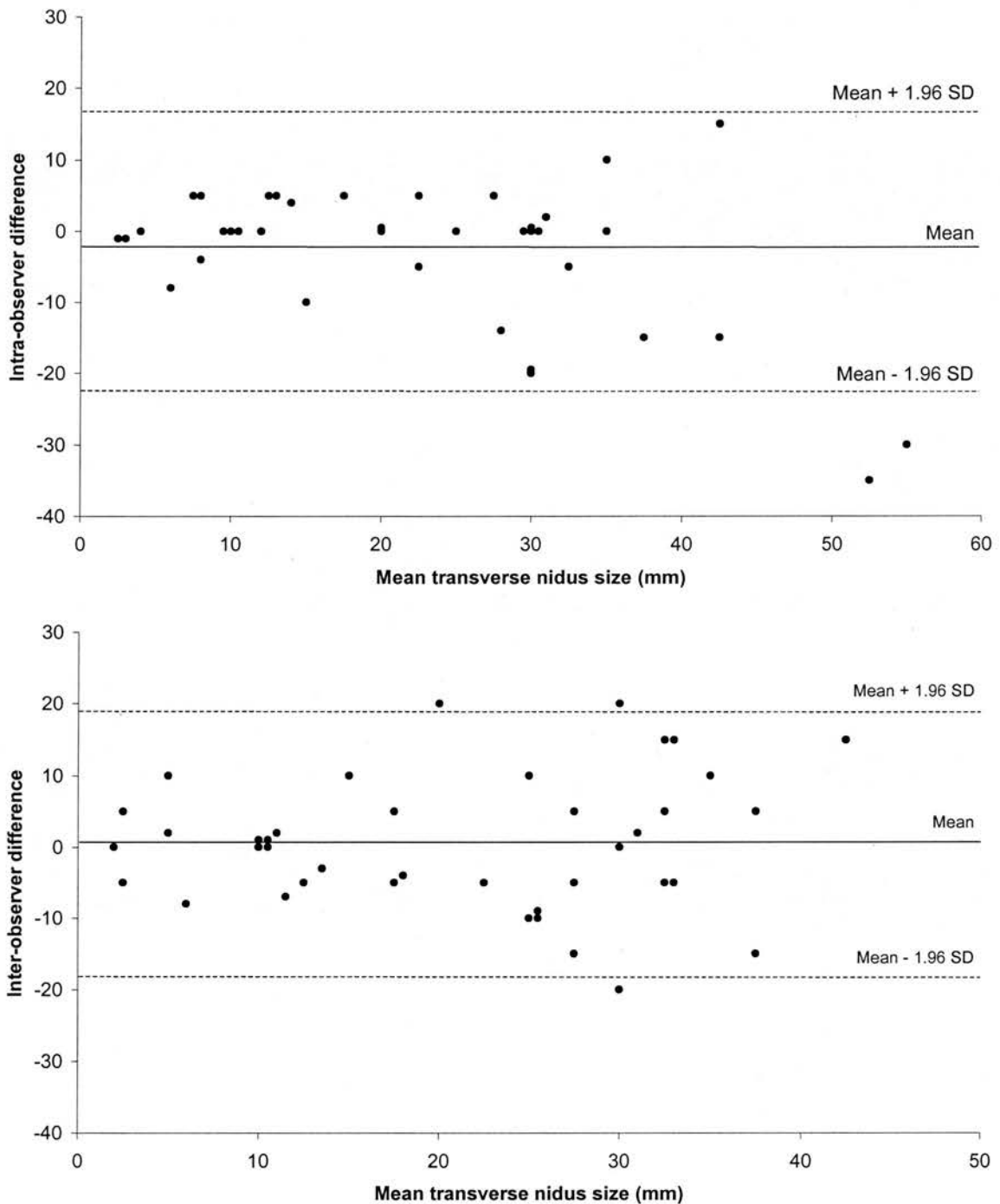


Figure 36 Anteroposterior (top) and lateral (below) projections of a right carotid intra-arterial digital subtraction angiogram which show a right frontoparietal AVM

There was agreement that this AVM was a simple fistula of Spetzler-Martin grade II, lacking many angioarchitectural features. However, there was disagreement about whether there were one or two feeders (dashed arrow) and whether there was a nidal aneurysm or venous varix (solid arrow)

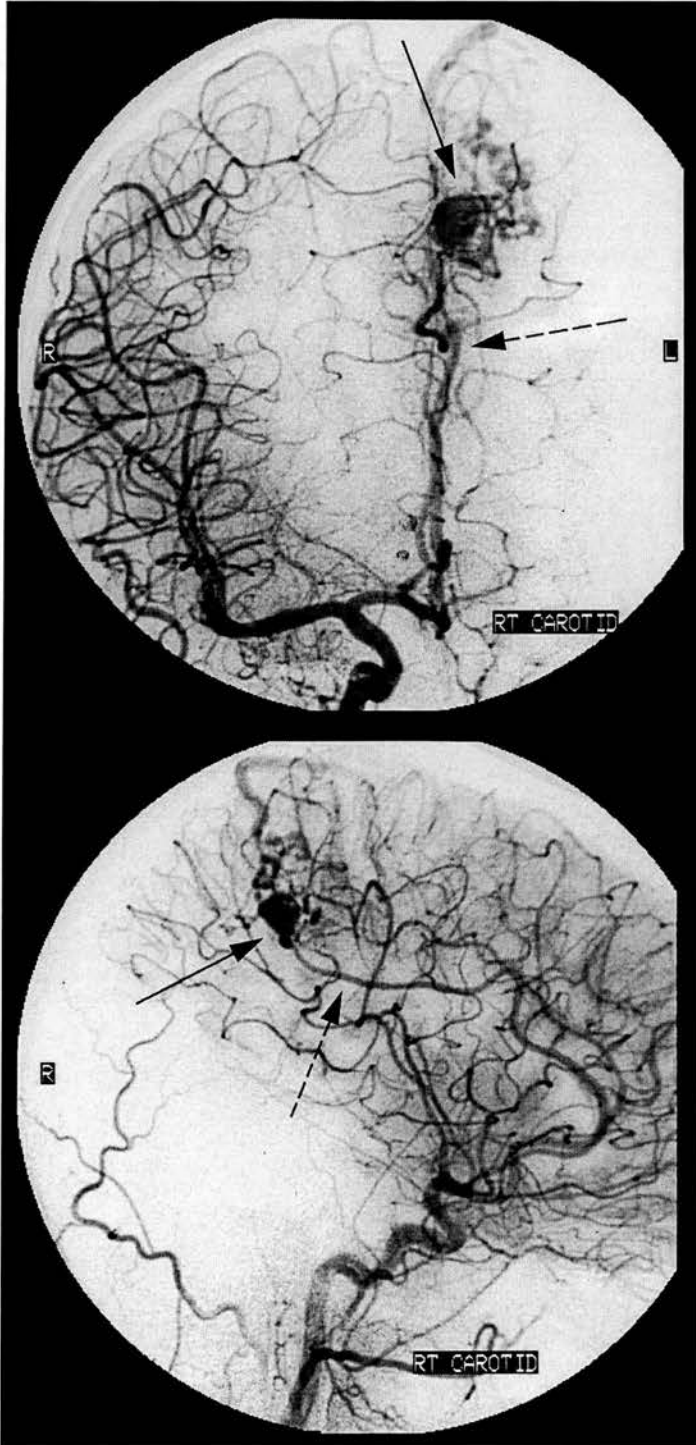
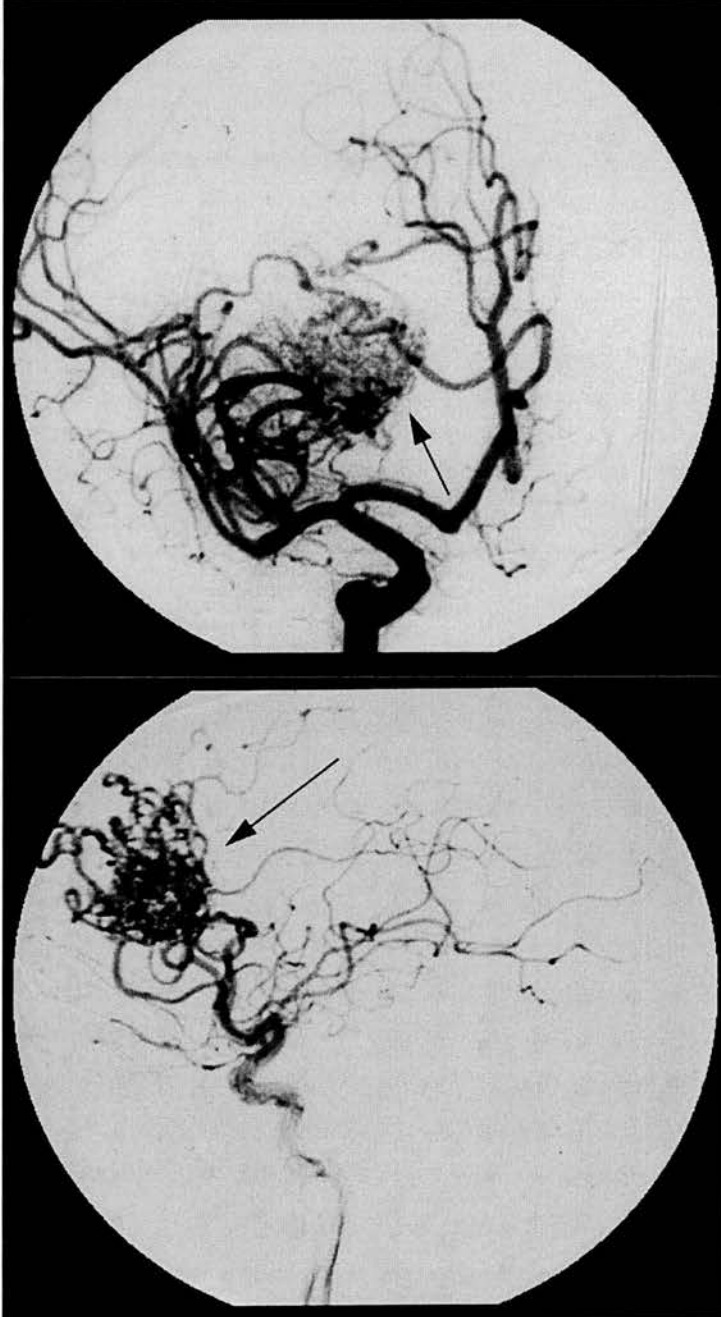


Figure 37 Anteroposterior (top) and lateral (below) projections of a right carotid intra-arterial digital subtraction angiogram which show a right frontal AVM (arrow)

There was disagreement about whether the nidus was greater or less than 30mm in all dimensions, number of feeders, type of feeding artery angiopathy, presence of angiogenesis, existence of collaterals, nidus border, discernible fistula in the nidus, number of draining veins, Spetzler-Martin grade, venous ectasia and existence of nidal aneurysms



Section 4: The frequency and clinical presentation of arteriovenous malformations of the brain in Scotland

- Chapter 11 The point prevalence of arteriovenous malformations of the brain in the Lothian healthboard region of Scotland
- Chapter 12 The Scottish Intracranial Vascular Malformation Study (SIVMS) – incidence of arteriovenous malformations of the brain
- Chapter 13 The Scottish Intracranial Vascular Malformation Study (SIVMS) – clinical presentation of arteriovenous malformations of the brain
- Chapter 14 The Scottish Intracranial Vascular Malformation Study (SIVMS) – radiological features of arteriovenous malformations of the brain

Chapter 11. The point prevalence of arteriovenous malformations of the brain in the Lothian healthboard region of Scotland

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11.1 Introduction

From my systematic review of the literature (Chapter 2), I knew there were no community- or population-based studies specifically investigating brain AVM prevalence [Berman *et al.* 2000; Al-Shahi and Warlow 2001]. Hospital-based post mortem series have reported brain AVM prevalence up to ~600 per 100,000, but these estimates must have been considerably biased by the method of cohort selection and the thoroughness of lesion ascertainment [Sarwar and McCormick 1978; Courville 1950; Jellinger 1986]. A community-based study found the point prevalence of the whole spectrum of IVMS to be 19 (95%CI 10 to 27) per 100,000 on 1 January, 1990 [Brown, Jr. *et al.* 1996b], from which an upper limit for brain AVM prevalence of ~10 per 100,000 had been inferred [Berman *et al.* 2000].

The size of the study population and the methods of case ascertainment affect prevalence estimates. Although larger studies produce more precise estimates they are likely to miss cases (unless incredibly well resourced), whereas thorough ascertainment is more feasible in smaller studies which inevitably produce less precise estimates. Whilst common diseases such as stroke are amenable to extensive surveys of population samples for the disease [O'Mahony *et al.* 1999], rarer disorders such as brain AVMS require targeted surveillance of the parts of the healthcare system actively involved in their management and/or passive inspection of secondary data sources.

Therefore, I sought to estimate the prevalence of brain AVMS in a sizeable adult population of a geographically and demographically well-defined community in Scotland, using active surveillance of clinicians involved in the care of such people, as well as passive case ascertainment from routinely-collected data. It would have been an overwhelming effort to undertake a Scotland-wide prevalence study as part of SIVMS. Instead, I chose the Lothian healthboard as the study area, because the population would be a manageable size for such a study, and being based at the regional neuroscience centre meant the study would be logistically easier.

11.2 Methods

11.2.1 *Inclusion criteria*

I included adults who were aged 16 years or over and permanently resident in the Lothian health board area of Scotland on 30 June 1998, and who had been diagnosed with a brain AVM prior to this prevalence date. The brain AVM definition I used was the same as SIVMS, not requiring IADSA for a definite diagnosis (3.2.3, page 98).

11.2.2 *Exclusion criteria*

I excluded people who did not fully meet the inclusion criteria above, and those with pure vein of Galen malformations, dural AVMs or any other type of IVM occasionally confused with a brain AVM [Chaloupka and Huddle 1998].

11.2.3 *Study setting*

The Lothian health board covers 700 square miles in South East Scotland, ranging from the Pentland Hills to the shores of the Firth of Forth and the North Sea, including the capital city, Edinburgh. The health board area is geographically defined by postcodes, enabling clear criteria for residency within the community. Although the most recent decennial census in Scotland was conducted in 2001, the results were not available at the time of analysis. Between censuses, the GRO estimates the size and age structure of the Scottish population annually using registration of births and deaths as well as immigration and emigration data. The estimated population of the Lothian health board on 30 June 1998 was 773,700, of whom 628,788 were ≥ 16 years of age. The stability of the whole population is reflected by a flux of only 0.2% over the year leading up to 30 June 1998, mostly attributable to 8,892 births, 8,157 deaths and 665 estimated net civilian migration.

The study was based at the regional neuroscience centre (Western General Hospital) in Edinburgh, which serves the population of the Lothian health board (and others), and

provides the only specialist brain AVM clinic for the South East of Scotland. Few residents receive health care in England – except on a quaternary referral basis – and there is little cross boundary flow of the population for health care, which minimises missing diagnoses made outside Scotland. Almost every patient is registered with a GP. Virtually all healthcare is accessed via the National Health Service (NHS), and patients diagnosed in private practice are usually referred to the NHS specialist brain AVM clinic (sic). Apart from the usual facilities for rehabilitation, there are no particular services that would lead to the Lothian healthboard harbouring an excess of disabled people.

ISD in Scotland has centrally registered every person discharged from a NHS hospital since 1980, collated the GRO's death certificate records, and coded main and subsidiary diagnoses using versions ICD-9 and ICD-10. These databases are available to research studies with ethics committee approval. Several mechanisms for ensuring data quality are in place at ISD, including validation, accreditation, quality assurance and monitoring, and national coding advice and training programmes [Harley and Jones 1996].

11.2.4 *Study design*

I used multiple overlapping sources of case ascertainment to identify adults meeting the inclusion criteria.

11.2.4.1 Collaborative neuroscience network

I approached all consultant neurologists, neurosurgeons and stroke physicians covering the study area, who were also part of SIVMS's collaborative network in order to obtain lists of their patients meeting the inclusion criteria. I also searched the diaries from 1995 until 2000 of the specialist brain AVM clinic operating at the regional neuroscience centre.

11.2.4.2 General practitioners

I wrote to all 557 GPs at the 101 general practices in the study area in 1999, requesting details of adults registered at the practices who met the inclusion criteria. I pre-supposed that GPs would find such people memorable, as each GP was unlikely to look after

more than one person with a brain AVM. I was unable to search GPs' patient databases due to the inadequate coding of brain AVMs in their 'Read' coding system and because of changes in UK data protection legislation and confidentiality guidance at the time of this study (Chapter 17).

11.2.4.3 Routine coding of hospital discharge data

In early 2000, colleagues at ISD searched the national database of hospital admissions and discharges (SMR01). They identified every adult who was alive on the prevalence date, and who had been discharged from a Scottish hospital to an address in the Lothian health board at any time since 1980 with an ICD code for a brain AVM (ICD-10 codes I60.8 and Q28.2; ICD-9 codes 430 and 747.8).

11.2.4.4 Data collection and validation

All available case notes, brain imaging and pathology reports were reviewed to validate each person's brain AVM diagnosis, and ensure they were alive, at least 16 years of age and resident in the geographical area of the study on the prevalence date of 30 June 1998. Brain/vascular imaging and/or pathology reports were available in every case. Residence was determined by comparing an adult's home postcode on the prevalence date with a database of all the postcodes defining the Lothian health board. I had no difficulty in matching duplicate notifications of adults between the sources, using first name, surname and date of birth, in the absence of any other unique identifier.

11.2.5 *Statistical analysis*

I calculated crude prevalence as the proportion of the adult (aged ≥ 16 years) mid-year population estimate for the Lothian health board that was known to fulfil the inclusion criteria on the prevalence date. Age-standardised prevalence estimates were directly age-adjusted to the last census in the UK in 1991 (<http://www.census.ac.uk>) and the last census in the USA in 2000 (<http://factfinder.census.gov>). 95% confidence intervals around prevalence estimates were based on the Poisson distribution, and were calculated using Confidence Interval Analysis software [Altman *et al.* 2000]. Tests for statistical

significance were performed in Statistical Product for the Social Sciences (SPSS) version 10.0.5. Statistical Analysis Software (SAS) version 8 was used for capture-recapture analysis (11.3.4, page 232).

11.3 Results

11.3.1 Recruitment

In total, 148 people were identified by the three sources of case ascertainment as potentially meeting the study inclusion criteria. Of these people, medical records were missing in four, 51 were excluded, mainly because they were resident outside the Lothian health board, leaving 93 adults included in the study (Figure 38, page 240).

11.3.2 Baseline characteristics

Of those included, 53 were men and 40 were women. Men were significantly younger on the prevalence date than women (median age 39 years versus 51 years, $p=0.003$), for no apparent reason (Table 19, page 237). The majority (77%) had been investigated with IADSA, usually in combination with axial brain imaging (Figure 39, page 241). Nine adults (10%) had co-existing aneurysms, and this proportion might have been greater had all adults had IADSA. 58 (62%) of 93 brain AVMs were located in so-called eloquent areas (Table 20, page 238), according to the Spetzler-Martin grading scheme's determination of eloquence (hypothalamus, thalamus, brain stem, cerebellar peduncles, and sensorimotor, language and visual cortex) [Spetzler and Martin 1986]. Every brain AVM was solitary, and did not occur in combination with any other IVM. There was radiological evidence of therapeutic obliteration of the AVM in 25 (27%) adults.

11.3.3 Prevalence

93 adults had been diagnosed with a brain AVM at some time during their life and were living in the Lothian health board on 30 June 1998, giving a crude prevalence of 14.8

(95%CI 11.9 to 18.1) per 100,000 adults. Age- and sex-specific prevalences are shown in Figure 40, page 242; males were more prevalent in younger age groups, accounting for their lower median age at diagnosis, although the 95% confidence intervals of the sex-specific prevalence estimates overlapped in each mid-decade age band. Prevalences directly age-adjusted to the GB 1991 census population and the USA 2000 census population were 14.6 and 14.7 per 100,000 adults respectively.

11.3.4 *Adjustment for incomplete case ascertainment*

Figure 41 (page 243) demonstrates the degree of overlap between the study's three major sources of case ascertainment. Routine coding of hospital discharge data was the most productive source, identifying 70 (75%) cases, followed by hospital consultants and AVM clinic diaries (52%) and GPs (39%). There was a sizeable overlap between sources, with 47 (51%) adults identified by at least two sources. I have used capture-recapture analysis to estimate the number of people potentially missed, based on the observed overlap between the three sources of case ascertainment [Hook and Regal 1995]. I presupposed that the sources would be dependent but to varying degrees, and that there was most likely to be dependence between hospital consultants/diaries and routine coding, because of the derivation of the latter from the former.

There are eight possible log-linear models, each with a different configuration of dependencies between three sources of ascertainment (Table 21, page 239). The residual deviance is a measure of the 'goodness of fit' of each model, when compared to the model in which all sources are assumed to be dependent; the better the fit, the lower the residual deviance. The model I chose had the lowest residual deviance, and estimated that 20 (95%CI 7 to 55) prevalent adults were missed by the study. The coverage (or completeness) of the study – calculated from the number of cases observed (93) as a proportion of the cases expected on the basis of capture-recapture analysis (100 to 148) – was 63% to 93%. By including this estimate of 20 missed cases, the ascertainment-adjusted brain AVM prevalence was 18 (95%CI 16 to 24) per 100,000 adults.

11.4 Summary

- In this first community-based study of brain AVM prevalence, I found a crude prevalence of 15 (95%CI 12 to 18) per 100,000 adults
- The prevalence may be as high as 18 (95%CI 16 to 24) per 100,000 adults if capture-recapture analysis is used to estimate the number of cases missed by my ascertainment process
- Therefore, in the year 2000, adults with a brain AVM numbered between 650-1,000 in Scotland, 7,600-11,400 in the United Kingdom and 35,400-53,000 in the USA

11.5 Discussion

This study illustrates the burden on the public health of a condition which has potential long-term risks of recurrent ICrH and epilepsy, as well as other disability, and which attracts expensive interventional treatments. These estimates have implications for the planning, purchasing and provision of health services for people with a brain AVM.

11.5.1 *The nature of brain AVMs*

Brain AVMs themselves pose several challenges for epidemiological studies. The people who are diagnosed are probably an inherently biased group, as the suspicion of an underlying brain AVM and the use of investigations to identify it depends on aspects of the patient and their presentation. Younger people with recurrent ICrH, recurrent and/or focal epilepsy and atypical headache are more likely to be investigated. Regional investigation practices amongst neurologists, neurosurgeons and neuroradiologists will further influence these biases, as will the availability of non-invasive brain imaging and IADSA. Moreover, any prevalence estimate will also be affected by historical patterns of investigation – the paucity of elderly people in the sample is undoubtedly affected by the reliance on IADSA for diagnosis before the 1970s, when CT was introduced.

These same factors will influence the detection of asymptomatic brain AVMs. The number of asymptomatic brain AVMs at any one time remains in some senses

imponderable, because the development of brain AVMs is likely to be dynamic – they are not necessarily congenital [Lasjaunias 1997]. Although published studies of asymptomatic volunteers undergoing MRI have not detected asymptomatic brain AVMs [Yue *et al.* 1997; Katzman *et al.* 1999], a ‘brain check-up’ system in Japan has found, using MRA, 3 (0.1%) of 3085 apparently healthy people (mean age 55 ± 11 years, male: female ratio 2:1) to harbour a brain AVM (Yukito Shinohara, Tokai University School of Medicine, personal communication). The asymptomatic brain AVM prevalence in Japan is an order of magnitude greater than brain AVM (symptomatic and asymptomatic) prevalence in Lothian, but comparison of the two studies is difficult because the Japanese study was clearly not population-based.

11.5.2 *Methodological biases*

This study is best regarded as providing a minimum estimate of brain AVM prevalence. Whilst complete ascertainment and overlap between sources would be desirable, it is virtually impossible in any study of a large population. My estimate of 63-93% completeness (based on capture-recapture analysis) appears reasonable. The extent of intersection of my sources of ascertainment will have been affected by: the number of adults admitted to hospital and so included in routine coding; the accuracy of hospital discharge data and ICD coding; the thoroughness of GP, consultant and AVM clinic records; and the extent of clinicians’ memories. The absence of any other feasible, local sources of case ascertainment make this study difficult to improve upon. Perhaps a future cross-sectional analysis of the SIVMS cohort would be more precise, and so have good statistical power to detect any future change from this contemporary prevalence estimate.

11.5.3 *Capture-recapture analysis*

Capture-recapture methods were originally developed by ecologists for censuses of wildlife. Animals are captured, tagged, released back into the wild, and the process repeated (re-captured). The total size of the animal population is estimated from the proportion of animals that were tagged by the first capture and ‘recaptured’ by the

second. The parallels with epidemiological studies using several sources have resulted in widespread, albeit controversial, use of the technique [Hook and Regal 1995; Papoz *et al.* 1996]. Capture-recapture analysis has been particularly useful for estimating the frequency of neurological conditions, because it minimises the cost of exhaustive methods of case ascertainment and prevents under-estimation of disease frequency [Taub *et al.* 1996; Martyn 1998]. However, the results of capture-recapture analysis must be interpreted and presented with caution [Hook and Regal 1999], because the assumptions inherent in the technique do not always hold in human populations [Papoz *et al.* 1996; Martyn 1998; Tilling 2001].

The technique requires that the population size is constant (i.e. there are no changes due to birth, death or migration), that members of the population under study can be recognised and are equally 'catchable', and that the sources of ascertainment are independent to enable the use of asymptotic statistical theory. Although study of a fixed population is impossible, stable populations – such as the Lothian health board – are an adequate approximation. In the healthcare setting, sources of ascertainment are usually dependent to varying degrees; for example, inclusion in one source (hospital consultant and AVM clinic records) confers inclusion in another source (routine coding of hospital discharge data). Such positive dependency between two sources could underestimate the number of people missed. Certain aspects of individuals may make them more likely to be ascertained by one source than another (for example, people investigated as outpatients who are not thought to require treatment are more likely to be identified by GPs than by AVM clinic diaries). Such negative dependency between sources could overestimate the number of people missed. The assumption of equal 'catchability' rarely holds, because severely affected individuals are more likely to be captured [Taub *et al.* 1996]. Therefore, the estimate of the total population of adults with brain AVMs may be biased by assuming that the missing cases resemble the ascertained ones.

Whilst capture-recapture analysis is most straightforward using two sources, the above complexities of human populations have attracted methods using more than two sources and log-linear modelling of source dependencies [Hook and Regal 1995]. It is generally held that three sources are ideal in epidemiological studies. Clearly the number of missing people is sensitive to the choice of model (Table 21, page 239). I chose the most parsimonious model that did not assume dependence between all three sources,

but modelled dependence between GPs and the hospital source, as well as the dependence I had presupposed to exist between the hospital source and routine coding. This latter dependence was expected in practice, because routine coding is derived from records of hospital admissions. In the chosen model, the other dependence (between GPs and hospital-based sources) is unsurprising, given the reliance on hospital-based investigations for brain AVM diagnosis.

A recent approach to address the influence of patient characteristics which may affect the probability of capture by different sources (for example, demographics and disease severity), has been to stratify patients by these characteristics or use a multinomial logit model to identify and account for them [Taub *et al.* 1996; Tilling and Sterne 1999]. This is an approach I would have used, were it not for the unavailability of the complete medical record in every case.

Table 19 Baseline characteristics of 93 prevalent adults with brain arteriovenous malformations

Characteristic	
Prevalent adults	93
Males (%)	53 (57)
Median age on the prevalence date (25% and 75% quartiles) in years	
Male	39 (30 - 53) *
Female	51 (44 - 65) *
Co-existing aneurysms	
Nidal	2
Feeding artery	6
Remote	1
	} 9 (10%)
Radiological evidence of AVM obliteration following treatment (%)	25 (27)

* p=0.003 (Mann-Whitney U test)

Table 20 Principal locations of the 93 brain arteriovenous malformations, their laterality and so-called eloquence (asterisked) according to the Spetzler-Martin grading scheme [Spetzler and Martin 1986]

Location	Side		
	Left	Midline	Right
Frontal	6*	1	6
Fronto-temporal	-	-	2
Fronto-parietal	3*	-	2*
Temporal	7 (4*)	-	9
Temporo-parietal	4*	-	4
Parietal	10*	-	15*
Parieto-occipital	5	-	4
Occipital	4*	-	
Thalamus	1*	-	2*
Medulla	-	1*	-
Cerebellum	2*	1	4*
Total (%)	42 (45%)	3 (3%)	48 (52%)

Table 21 Eight different log-linear models for 3-source capture-recapture analysis, accompanied by the residual deviance and estimated number of missing cases (with 95% confidence interval) for each model. The chosen model is marked with an asterisk.

Model (source dependence illustrated by –)	Residual deviance	Cases missed (95%CI)	
Independent	2.4	13	(7 to 23)
GP – Hospital	1.0	15	(8 to 29)
Hospital – Coding	2.4	14	(6 to 33)
GP – Coding	2.4	13	(6 to 28)
GP – Hospital & GP – Coding	0.9	17	(7 to 39)
GP – Hospital & Hospital – Coding *	0.7	20	(7 to 55)
Hospital – Coding & GP – Coding	2.3	15	(4 to 56)
Hospital – Coding & GP – Coding & GP – Hospital	0	34	(7 to 172)

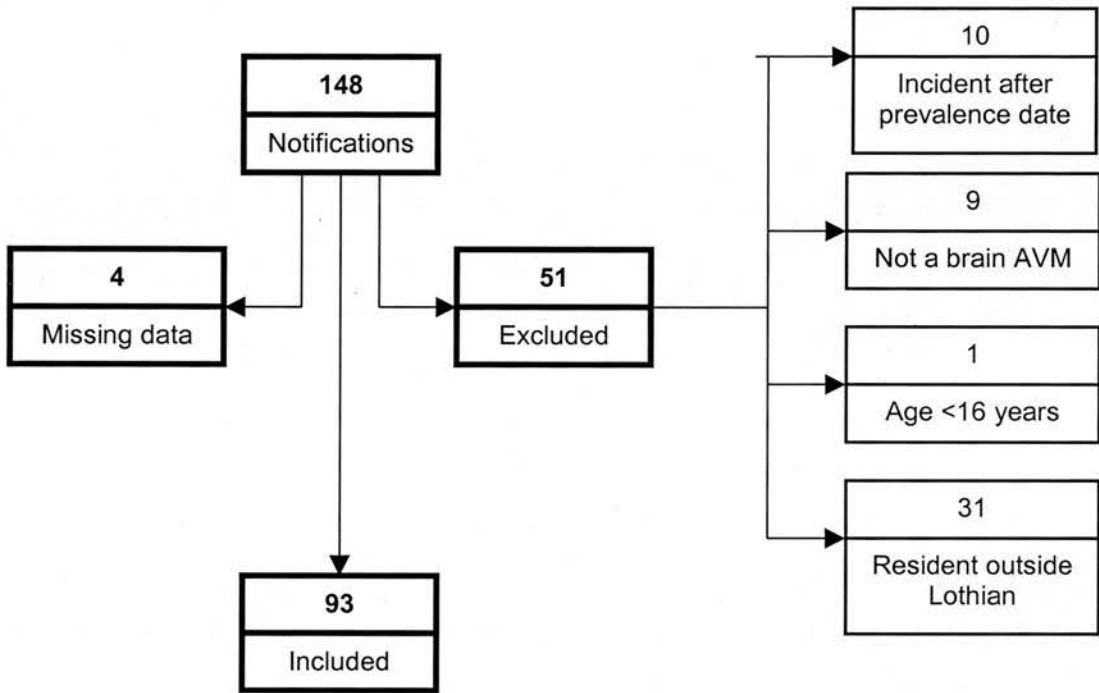
Figure 38 Flow diagram of people notified to the study

Figure 39 Venn diagram illustrating the radiological investigations that led to a definite diagnosis of a brain arteriovenous malformation in the 93 prevalent adults

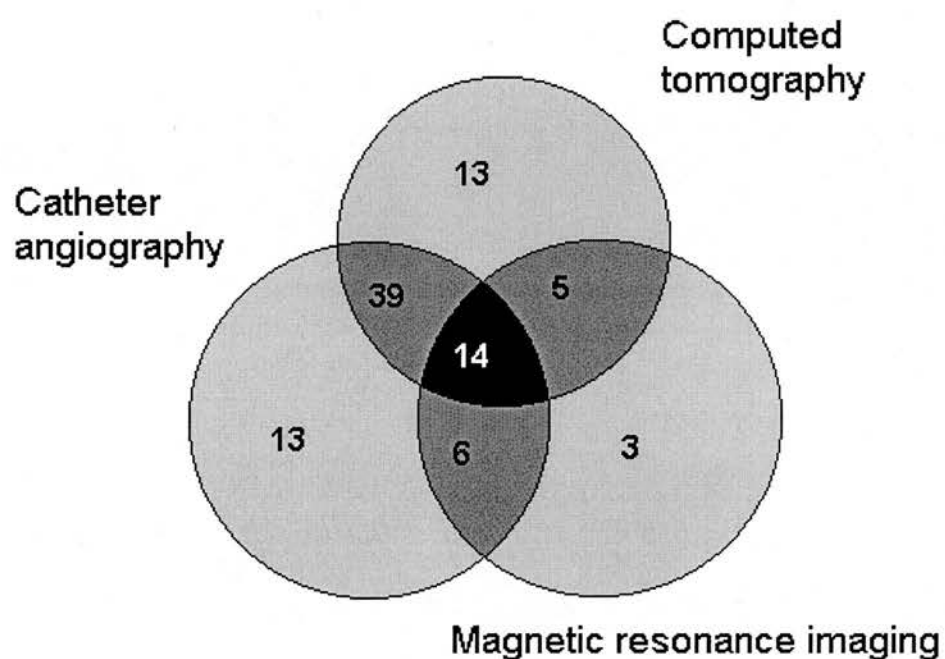


Figure 40 Age- and sex-specific crude point prevalences for adults with brain arteriovenous malformations, with lower 95%CI (women, closed boxes) and upper 95%CI (men, open boxes)

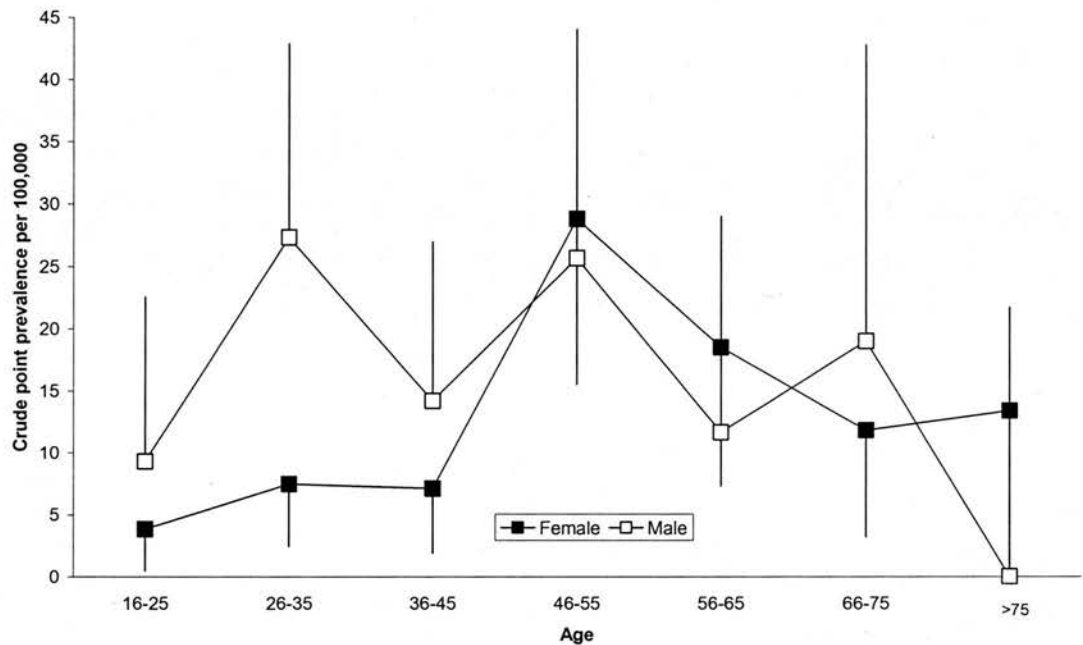
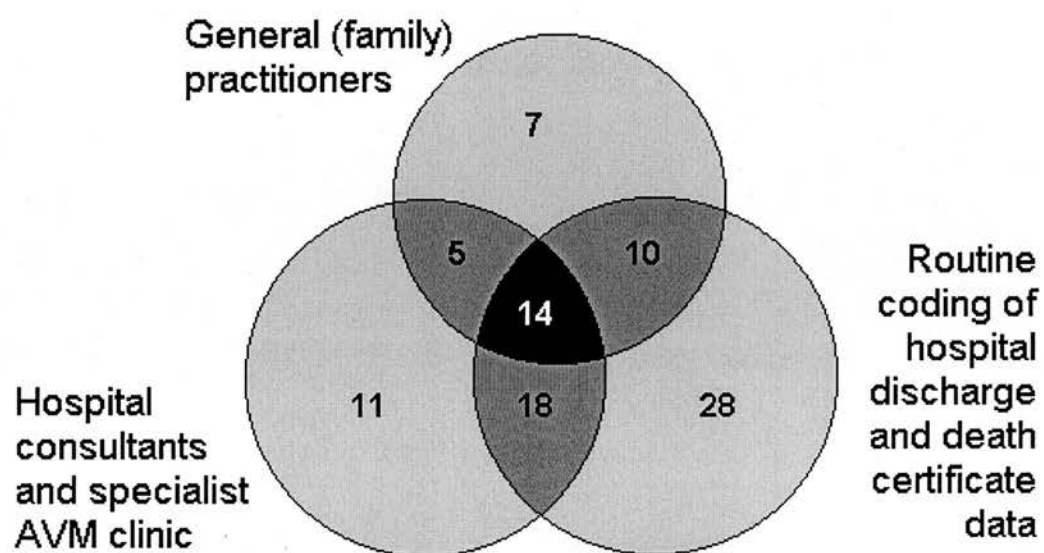


Figure 41 Venn diagram of overlap between the sources of case ascertainment of the 93 prevalent adults



Chapter 12. The Scottish Intracranial Vascular Malformation Study (SIVMS) – incidence of arteriovenous malformations of the brain

Chapter contents

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 - 12.3.3 Crude incidence
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- 12.4 Summary
- 12.5 Discussion
 - 12.5.1 Incidence versus detection
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 - 12.5.3 Potential biases and limitations

12.1 Introduction

Ideally, accurate estimates of incidence should be based on complete, prospective ascertainment from a large, well defined, stable population, or a representative sample of one (2.2.2.1, page 58). These studies should have external validity by sharing standard definitions, methods and data presentation to make them comparable [Sudlow and Warlow 1996; Joint Writing Group 2001; Al-Shahi and Warlow 2001]. In this way, they will not only describe the incidence and clinical and radiological characteristics of AVMs, but also provide population-based estimates of prognosis with prospective follow-up, leading to derivation and testing of prognostic models, and potentially provide a cohort for case-control studies and recruitment into randomised controlled trials [Al-Shahi and Warlow 2003].

Hospital-based studies will not suffice. Until recently (Chapter 11), prevalence estimates have been derived from hospital-based autopsy series, but these are subject to each institution's frequency of post mortem examination and various referral/selection biases, as well as the special interests – and so meticulousness – of the pathologists [Berman *et al.* 2000]. Hospital-based studies – especially those from tertiary referral centres – are also unrepresentative of the population because they tend to miss both sudden deaths in the community and people who are not thought to warrant hospital admission (be they asymptomatic or unsuitable for treatment). Moreover, there is a growing appreciation of the long-suspected differences between these hospital-based series, likely to reflect regional investigation and referral patterns, specialists' access to and interest in particular interventional treatments, and varying classifications used by research groups [Hofmeister *et al.* 2000; Halim *et al.* 2002; Al-Shahi *et al.* 2002b].

Until SIVMS started, there had been only one truly population-based study of brain AVM incidence (2.3.1.1, page 61). I hypothesised that the incidence of brain AVMs in SIVMS might be higher because of both the increasing availability and uptake of brain imaging since the older study and because of the thoroughness of case ascertainment in SIVMS (8.2, page 188).

12.2 Methods

The first two complete years (1999-2000) of SIVMS have been used to calculate the incidence of brain AVMs amongst adults meeting the SIVMS inclusion criteria (3.2.1, page 97).

The crude incidence was calculated cumulatively for 1999 and 2000 as the proportion of the adult (aged ≥ 16 years) mid-year population estimate for Scotland that was detected as having a brain AVM during that year.

Ideally, the incidence calculation should remove prevalent people from the denominator. I did not do this, because the number of prevalent people was likely to have been so small, based on my prevalence study (Chapter 11), as to make a negligible impact on the incidence.

95% confidence intervals around incidence estimates were calculated according to the Poisson distribution [Altman *et al.* 2000]. Age-standardised incidence estimates were directly age-adjusted to the 1991 census in Great Britain (<http://www.census.ac.uk>) and the last census in the United States of America in 2000 (<http://factfinder.census.gov>).

12.3 Results

12.3.1 Notifications

Figure 42 (page 252) illustrates the recruitment of adults with definite and uncertain (probable or possible) brain AVMs to SIVMS from 1st January 1999 to 31st December 2000 inclusive. The collaborative nation-wide network notified the largest number of people to SIVMS, followed by routine coding of hospital discharge data and death certificates. Scotland's GPs contributed so few eligible people in 1999 who were as yet unknown to the study, that I abandoned this source in the second and subsequent years of the study. Of 418 notifications, 190 (45%) were eligible and included in SIVMS, 96 of whom (23% of all notifications) had definite, probable or possible brain AVMs.

12.3.2 *Definite brain AVMs*

Following review of diagnostic brain imaging, reports of pathological examinations and case notes, 92 (96%) of the 96 included adults were deemed to harbour a definite brain AVM (Figure 42, page 252). There was an increase in the number of definite cases detected from 44 to 48 between 1999 and 2000, which was not statistically significant, with a concomitant rise in the mid-year adult population estimate for Scotland from 4,110,956 to 4,114,052.

12.3.3 *Crude incidence*

The crude incidence of definite brain AVMs in Scottish adults in 1999 and 2000 was 1.12 (95%CI 0.90 to 1.37) per 100,000 adults per year (Figure 43, page 253). The incidence of symptomatic definite brain AVMs was 0.89 (95%CI 0.70 to 1.12) per 100,000 adults per year and the incidence of asymptomatic (incidentally discovered) brain AVMs was 0.23 (95%CI 0.14 to 0.36) per 100,000 adults per year. A detailed description of the modes of presentation is provided in Chapter 13.

12.3.4 *Age- and sex-specific incidence*

There does not appear to be a significant difference in incidence between sexes and mid-decade age bands (Figure 44, page 254). There appears to be a tendency towards a peak incidence in the 46-55 year age group, although the detection of only 92 adults has meant that precision is inevitably low and 95%CIs overlap.

12.3.5 *Standardised incidence*

Age-standardised incidences directly age-adjusted to the last decennial censuses in Great Britain and the USA were essentially the same as the crude estimate of incidence. The age-standardised brain AVM incidence, directly age-adjusted to the 1991 census population of Great Britain (England, Wales and Scotland, but not Northern Ireland) was 1.10 per 100,000 adults per year. The age-standardised brain AVM incidence,

directly age-adjusted to the 2000 census population of the United States of America was 1.12 per 100,000 adults per year.

12.4 Summary

- In the years 1999 and 2000, SIVMS received 418 notifications from all sources of case ascertainment, of which 96 adults were included, and 92 had a definite brain AVM diagnosis
- The crude incidence of definite brain AVMs in Scottish adults was 1.12 (95%CI 0.90 to 1.37) per 100,000 adults per year
- The incidence of symptomatic definite brain AVMs was 0.89 (95%CI 0.70 to 1.12) per 100,000 adults per year
- The incidence of asymptomatic (incidentally discovered) brain AVMs was 0.23 (95%CI 0.14 to 0.36) per 100,000 adults per year

12.5 Discussion

It is clear from crude incidences that SIVMS has detected brain AVMs at comparable rates to other studies (Figure 43, page 253), notwithstanding SIVMS's focus on the adult (rather than the whole) population. Furthermore, the age-standardised incidences barely change when adjusted to the populations of the UK or USA (probably due the similarity of the Scottish population to their demographic structures). Therefore, the incidence of brain AVMs in SIVMS appears generaliseable; it is safe to conclude that in the areas of the USA, Europe and the Caribbean studied, brain AVM incidence is 1-1.5 per 100,000 per year.

It was interesting that brain AVM incidence did not differ significantly with age. I presupposed that brain AVMs would be detected at younger ages because of their tendency to present symptomatically in the fourth and fifth decades and the enthusiasm for investigating underlying causes of ICrH in the young. Equally, I would expect relative under-detection in the elderly, because symptomatic lesions would have been detected already and underlying causes of ICrH tend to be investigated less in the elderly on the grounds of their diminished life expectancy. Any inconsistency of the age-specific

incidence rates is, of course, masked by the imprecision of SIVMS. But part of the explanation for the comparability in incidence between age groups probably lies in SIVMS's population-based design finding incidental brain AVM diagnoses in the elderly, often missed by purely hospital-based studies. This is borne out by the tendency for incidental brain AVMs to present ~10 years later than symptomatic brain AVMs, as I shall describe in the next chapter.

12.5.1 *Incidence versus detection*

Strictly, incidence refers to the development of disease in a population initially free of it [Sackett *et al.* 1991; Berman *et al.* 2000; Al-Shahi and Warlow 2001]. SIVMS will undoubtedly have missed as-yet-undiagnosed asymptomatic brain AVMs, which could be considered 'prevalent', and which may declare themselves – so becoming 'incident' – at a later date, or remain asymptomatic until death. Therefore, my quantification of incidence is a reflection of the rate of detection of brain AVMs. However, this is also true of many other diseases – for which the term incidence is used (such as the detection of asymptomatic cerebral infarction/haemorrhage on CT/MRI). I prefer the widely understood term 'incidence' to the more semantically correct 'detection rate'.

In this study there were 3 incidental brain AVMs identified amongst 14,630 post mortems conducted in Scotland between 1999-2000 (0.02%), although these will have been underascertained. In any case, the number of asymptomatic brain AVMs at any one time remains imponderable, because of their likely dynamic development and the *de novo* appearance of some types [Lasjaunias 1997; Friedman *et al.* 2000].

Because the extent of detection of asymptomatic brain AVMs is undoubtedly affected by regional autopsy rates, the availability and resolution of brain imaging and the propensity of clinicians to use it, some prefer to adapt epidemiological terminology and describe detection rates, given that the number of truly 'incident' brain AVMs is immeasurable [Berman *et al.* 2000; Stapf *et al.* 2003]. The most meaningful comparison between studies is the detection rate of *symptomatic* brain AVMs, because they are the most clinically relevant. However, because of the tendency of some interventionists to treat brain AVMs regardless of their mode of presentation, a quantification of *asymptomatic* detection rate is also important.

12.5.2 *Comparison with other studies*

I suspected that SIVMS might find a higher brain AVM incidence than other studies because of the increasing use and availability of brain imaging over recent decades. However, rates were comparable and not significantly different, regardless of the year or design of the studies (Figure 43, page 253). I have found the proportion of symptomatic brain AVMs in SIVMS to be very similar to the Mayo Clinic study [Brown, Jr. *et al.* 1996b], and the detection rate of first-ever haemorrhage from a brain AVM to be very similar to the rate in the North Manhattan Stroke Study [Stapf *et al.* 2002]. The New York Islands Arteriovenous Malformations Study (NYIAVMS) (<http://cpmcnet.columbia.edu/dept/avm>) is an ongoing study – similar to SIVMS – which began in 2000, focuses on brain AVMs only, and is based on a population more mobile than Scotland with a $\geq 4\%$ annual flux at state and/or county level (<http://factfinder.census.gov>) [Stapf *et al.* 2003]. The overall brain AVM incidence described by NYIAVMS was also similar to SIVMS.

The similarity might be an artefact of under-ascertainment by SIVMS, although this would also have to apply to NYIAVMS, which is possible. All that remains for the further exploration of incidence is to monitor it in Scotland and elsewhere in the world, and to continue to try and improve methods of case ascertainment to see they impact upon incidence.

12.5.3 *Potential biases and limitations*

Design, regional biases and challenges posed by brain AVMs themselves will inevitably affect estimates of incidence.

Truly population-based studies may detect people missed by studies based at tertiary referral centres because their brain AVMs were not thought to warrant specialist attention or because their AVMs caused sudden death in the community from devastating ICrH. Regional variations in autopsy rates, the availability of neurologists, neurosurgeons and stroke physicians, and the availability of brain imaging will govern how headache, epilepsy and ICrH are investigated (3.2.4, page 101). SIVMS did not seek

every ICrH in Scotland, precluding an estimate of how many underlying brain AVMs might have been missed due to lack of investigation.

Brain AVMs themselves can be difficult to diagnose accurately given their occasional morphological overlap, the existence of AOVMs, and the perceived inappropriateness of definitive investigation of certain people, particularly the elderly. Moreover, the presence of an AVM underlying an ICrH can sometimes only be inferred because of the obliteration of a brain AVM nidus by the haemorrhage itself, leaving only clues to its cause, such as an early draining vein on IADSA. Furthermore, there will be an inevitable bias towards the detection of brain AVMs with a more aggressive prognosis, because people with recurrent haemorrhage or epilepsy following prior events (perhaps in the distant past) are more likely to have further or repeated investigation.

SIVMS has provided contemporary estimates of the incidence of brain AVMs in adults, which helps assess their public health importance. The study is also the foundation for future studies of the comparative epidemiology of all IVMs and their clinical course and prognosis. It remains to be seen whether recruitment and patterns of identification and presentation in SIVMS will remain the same; as larger numbers are recruited, the precision of my estimates will increase and significant dissimilarities could emerge. I plan to assess the cumulative incidence of brain AVMs with continued recruitment to the cohort (which will span a total of at least 5 years), paying particular attention to any trends in the detection of asymptomatic brain AVMs. Given the poor quality of existing studies of brain AVM prognosis, other population-based studies are essential for future evaluations of the clinical course of brain AVMs and the effects of their treatment, as are randomised controlled trials [Al-Shahi and Warlow 2003].

Figure 42 Recruitment of adults with brain AVMs to SIVMS, from notification to inclusion and determination of certainty of diagnosis

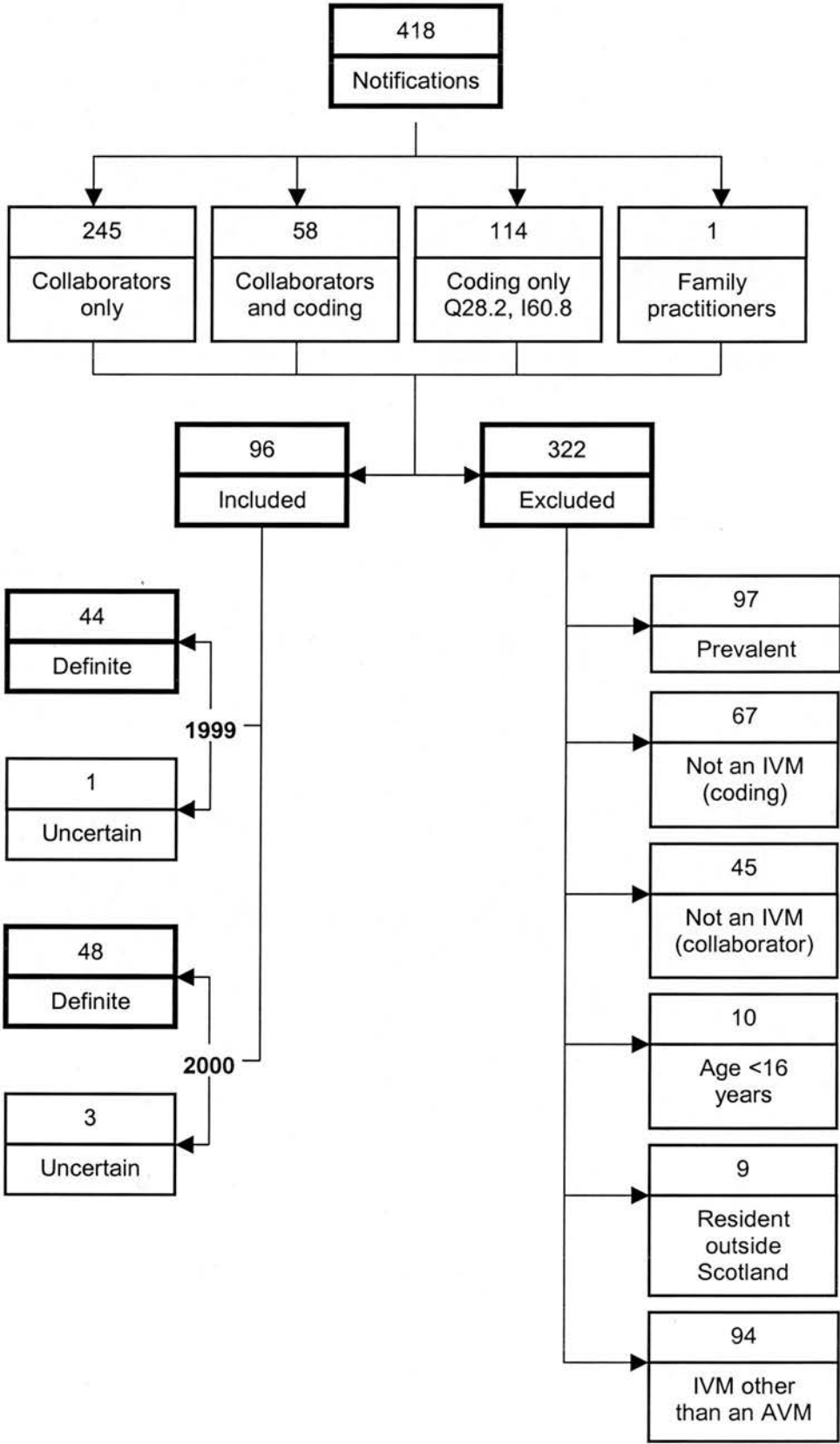


Figure 43 Crude incidence of brain AVMs amongst adults in Scotland (SIVMS), and other population-based studies, with 95% confidence intervals

The area of each point estimate box is proportional to the number of cases identified (enumerated above each box)

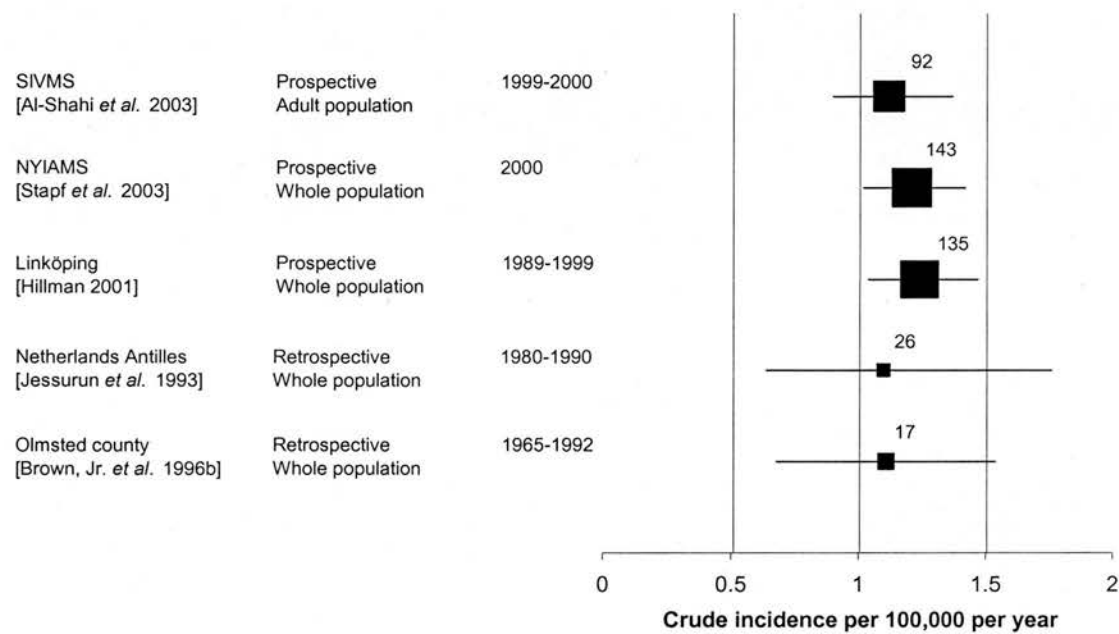
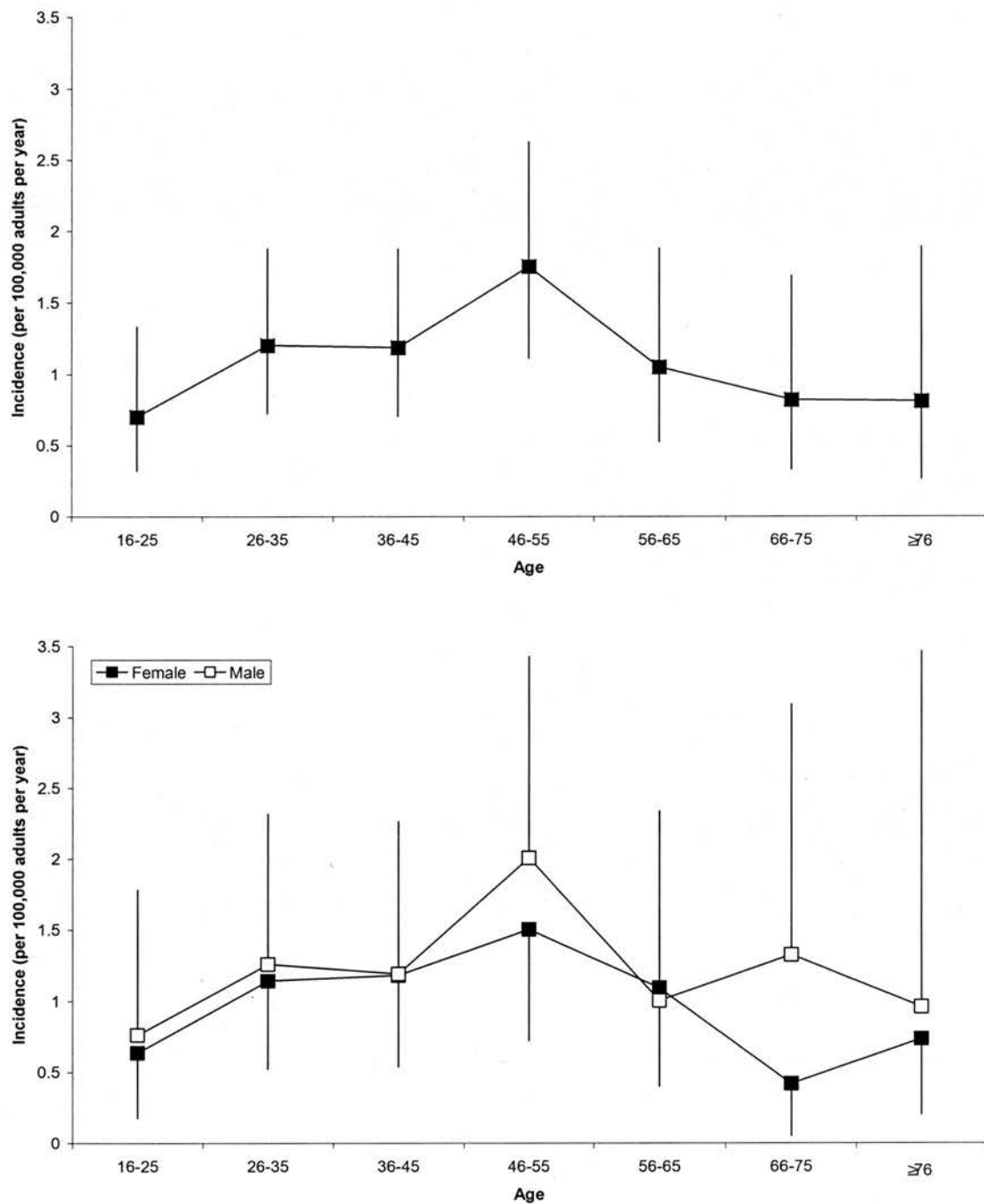


Figure 44 Age-specific incidence for brain AVMs with 95%CI's (above); age- and sex-specific incidence for brain AVMs with either upper or lower limit of each 95%CI shown for clarity



Chapter 13. The Scottish Intracranial Vascular Malformation Study (SIVMS) – clinical presentation of arteriovenous malformations of the brain

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 - 13.3.3.1 Overall pattern of presenting symptoms
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 - 13.3.3.4 Epilepsy
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 - 13.3.3.6 Incidental
 - 13.3.3.7 Disability at presentation
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 - 13.5.1 Characteristics of presentation
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 - 13.4.2.1 Other population-based studies
 - 13.4.2.2 Hospital-based studies
 - 13.5.3 Limitations of this study

13.1 Introduction

Having established the incidence of adults with brain AVMs, and segregated the incidence of symptomatic brain AVMs from the detection rate of incidental brain AVMs, in this chapter I will describe and explore how these adults came to medical attention. From my systematic review, I knew that a population-based study detected many more apparently incidental brain AVMs than hospital-based series (Figure 9, page 93), and others have described clear differences in the mode of presentation between separate tertiary/quaternary referral centres [Hofmeister *et al.* 2000]. These comparisons were not helped by the dearth of definitions of modes of clinical presentation in the literature, nor research groups' variation in allocating one, or more than one, mode of presentation. A painstaking description of presentation is likely to be relevant in both research and clinical practice, if the mode of presentation truly influences subsequent prognosis [Mast *et al.* 1997].

This chapter uses the definitions of presentation type and timing I set out in Chapter 3 and Chapter 5, relying on both clinical and radiological information, with only a single mode of presentation allocated to each adult. In the following chapter I will go beyond the radiological features of the mode of presentation, to elaborate upon the angioarchitecture of the underlying brain AVMs subsequently detected on IADSA.

13.2 Methods

The allocation of mode of presentation was made purely on the basis of case note and imaging review. Where typed discharge summaries did not provide sufficient information, I occasionally needed to copy the hand-written case record. However, no correspondence was entered into with clinicians to clarify further, often because so much time had elapsed between the initial presentation and the time I had received and reviewed the case notes. Whilst classification of haemorrhage type was made largely on the basis of axial brain imaging, classification of seizure type was often difficult because of the lack of an eyewitness account and a clear description of the symptoms. If seizure type subsequently became apparent following a neurological opinion, presentation type was amended accordingly.

13.3 Results

13.3.1 *Certainty of diagnosis*

In the years 1999-2000, 96 adults were included in SIVMS with a definite/probable/possible brain AVM. Of the 96, 92 had a definite brain AVM.

The four adults who could not be deemed definite possessed a possible or probable brain AVM, on the basis of their clinical presentation, imaging features and the lack of any other likely explanation for their state:

A 50 year-old man presented with a gradually progressive hemiparesis and was found to have a possible pontine brain AVM on MRI (Figure 45A-B, page 270). He had had a brainstem ICeH at the age of 42. No further imaging is planned (study number 143).

A 38 year-old man presented with complex partial seizures with secondary generalisation, and was found to have a possible brain AVM in the left callosal area on MRI and IADSA (Figure 45C-D, page 270), but follow-up IADSA was normal. No further investigation is planned (study number 347).

A 68 year-old man presented with persistent dizziness and diplopia, having suffered a brainstem haemorrhage two years beforehand. Re-evaluation with MRI revealed a probable AVM deep in the right pons (Figure 46A-B, page 271), but further imaging is not planned due to his level of disability (study number 376).

A 22 year-old woman presented with a left temporal ICeH. IADSA performed one and ten days later were normal, as was MRI two months after the haemorrhage. Diffuse capillary blush on follow-up IADSA 6 months after the ICeH was thought to suggest a brain AVM (Figure 46C-D, page 271), and she was referred for stereotactic radiosurgery. She was not treated because a further IADSA failed to demonstrate a brain AVM (study number 391).

Although all adults with definite, probable or possible brain AVMs are included in SIVMS, the rest of the analysis will be confined to the definite cases.

13.3.2 *Demographics*

Of the 92 adults with definite brain AVMs, 49 (53%) were male. The median age at presentation was 45 (inter-quartile range 22), range 16 to 81 (see Figure 44, page 254 for distribution). By early 2004, SIVMS had only succeeded in obtaining consent (and with it details about ethnicity) from 64 (70%) of the cohort: of these 64 adults, 1 (2%) was Chinese from Taiwan (but resident in Scotland), and 63 (98%) classified themselves as white, approximating to the ethnicity of the Scottish population (3.2.4.1, page 101).

13.3.3 *Clinical features*

I will describe the mode of presentation for the whole cohort (13.3.3.1 below), commenting separately on the subgroup that was dead at presentation and subsequently diagnosed at post mortem (13.3.3.2 below), and then elaborate on details of each mode of presentation.

13.3.3.1 Overall pattern of presenting symptoms

Of the incident brain AVMs, one fifth were incidental discoveries and four fifths were symptomatic (Table 22, page 267). Of the symptomatic cases, 43 (59%) were attributable to ICrH, 25 (34%) due to one or more seizure(s), and FNDs affected 5 (7%). Adults with brain AVMs that were detected incidentally were older (mean age 60 ± 15 years) than adults who presented with haemorrhage (mean age 42 ± 13 years), seizure(s) (mean age 40 ± 14 years), or FND (mean age 48 ± 16 years); these differences were significant ($\text{ANOVA}_{df=3} p=0.00001$).

13.3.3.2 Deaths at presentation

At the time of presentation, 4 (4%) of the 92 adults were dead. Of these, 3 were incidental discoveries at post mortem:

A 70 year-old man died from metastatic squamous cell carcinoma. He had an ischaemic stroke 7 years beforehand, but no prior symptoms from his right cerebellar brain AVM (patient 293).

A 77 year-old man died from cardiac failure and bronchopneumonia as a consequence of Wegener's granulomatosis. Nineteen years beforehand, he had an ICeH, followed 5 years before his death by a seizure disorder. Both the bleed and the epilepsy are likely to have been attributable to his left superficial temporal AVM, which was found at post mortem but never diagnosed in life (patient 329).

A 47 year-old woman died from an acute myocardial infarction. Five months prior to her death, she had presented with an ICeH, followed by generalised epilepsy. IADSA had been normal. At post mortem, apart from myocardial infarction, there was an organising haematoma in the posterior third of the right cerebral hemisphere, with an underlying right superficial temporo-occipital AVM (patient 360).

However, one death was deemed to be symptomatic. A 19 year-old woman died suddenly from a devastating ICeH, following general anaesthesia for excision of a pilonidal sinus. At post mortem the haemorrhage was found to be due to an AVM in the right basal ganglia, which hitherto had been asymptomatic.

13.3.3.3 Haemorrhage

Almost half of the 43 adults presented with a purely ICeH (Table 23, page 268). The next most common type was intraparenchymal with intraventricular extension and one eighth of adults with a bleed had a pure SAH.

The study neuroradiologists attributed all 5 cases of pure SAH to aneurysms associated with AVMs, rather than the AVM nidus itself. A presentation with pure SAH would guarantee subsequent IADSA, on which the morphology of one of the associated aneurysms and/or its proximity to the greatest accumulation of subarachnoid blood suggested to the study neuroradiologists that it had ruptured. However, in one of these 5 cases, the aneurysm thought to have bled was clipped, but at operation it did not appear to have ruptured. In these 5 cases of aneurysmal SAH associated with a brain AVM, the AVM itself *could* be regarded as asymptomatic, although I have regarded the nidus and its feeding and nidal aneurysms as an integral unit.

One woman presented with a haemorrhage, having had no prior symptoms, at the age of 34 years, when 32 weeks pregnant.

However, the allocation of a haemorrhagic mode of presentation was not always easy. Interestingly, in one adult who presented with what turned out to be an ICeH, CT of

the brain on the day of presentation did not reveal the bleed, but MRI 2 days later did. The more common scenario that left the occurrence of haemorrhage in doubt was when an adult would present with a run of seizures, and CT brain ≥ 10 days later left some doubt about haemorrhage. Usually the amount of oedema and density of the AVM nidus led us to diagnose a bleed when MRI was never performed.

13.3.3.4 Epilepsy

Of all adults presenting with seizure(s), in 11 (44%) they were generalised, in 8 (32%) they were simple partial \pm secondary generalisation, in 5 (20%) they were complex partial \pm secondary generalisation, and in one person the notes did not contain enough information to characterise the seizures. Confusingly, one adult with complex partial seizures \pm secondary generalisation had an ipsilateral superficial temporal lobe AVM, leading to me declare the AVM incidental (the notes left no doubt as to which side of the body was affected by the seizures).

13.3.3.5 Focal neurological deficits

Five adults presented with FNDs, in which symptoms and/or signs were attributable to the anatomic location of the AVM nidus, but there was no radiological evidence of haemorrhage.

Only one FND was persistent:

A 58 year-old woman presented with a sudden left temporal headache, nausea, difficulty reading and word-finding difficulty. On examination, she had a right upper homonymous quadrantonopia and right-sided hyperreflexia. She recovered gradually over several weeks, during which time she made spelling errors, she had many occipital headaches, and right-sided photopsia. CT brain two months after presentation and MRI brain after three months did not demonstrate blood products, although the MRI detected a left occipital corticoventricular AVM nidus and a small left frontal meningioma (patient 239).

Only one FND was progressive:

A 71 year-old man presented with progressive difficulty walking and impaired balance. CT brain one month later revealed right parietal

infarction in the vicinity of a right parieto-occipital AVM nidus, and MRI brain three months later confirmed this infarction with associated gliosis. The stroke physicians managing this case felt the AVM accounted for his symptoms, signs and the infarction (patient 221).

Three patients presented with transient FNDs:

A 39 year-old woman presented with sudden dizziness, slurred speech and falling to the right. Examination revealed nystagmus on left lateral gaze, but no other abnormalities. Her symptoms resolved within 24 hours. MRI brain one month after presentation revealed a small right frontal AVM with surrounding gliosis, but no evidence of haemorrhage or infarction (patient 265).

A 44 year-old man presented with sudden hemisensory symptoms affecting the left arm and leg, accompanied by a fluctuating headache, lasting less than 24 hours. Two months later, his sensory symptoms returned and became persistent, at which time MRI brain revealed a right thalamic AVM. Four months after presentation, he was treated with gamma knife radiotherapy; after another 18 months, his sensory symptoms became progressive, which were attributed to perinidal oedema following radiotherapy, and treated with oral dexamethasone (patient 282).

A 29 year-old woman presented with sudden slurred speech and dizziness lasting for less than a day. CT and MRI brain performed 6 and 7 months after presentation respectively revealed a right cerebellar AVM, without evidence of infarction or haemorrhage. Over the following two years, she underwent 3 embolisations which partially occluded the AVM nidus, and two weeks after the last one she developed increasing clumsiness, dysarthria, and right hand weakness, which was attributed to peri-nidal oedema by MRI brain (patient 363).

13.3.3.6 Incidental

Of the brain AVMs discovered incidentally, 3 were found at post mortem (13.3.3.2, page 258), and 16 were found on brain imaging. In 6 cases, the relationship of the presenting event to the AVM was unknown, and in the rest there was another clear explanation for it. The conditions that led to incidental detection were: ICeH (due to anticoagulation, not the AVM remote from the bleed), acute confusional states, epilepsy ipsilateral to the AVM, FNDs either anatomically remote from the AVM or not vascular in character, migraine, and a host of other symptoms (e.g. variable combinations of

sensorineural hearing loss, dizziness, tinnitus and unsteadiness leading to imaging 'to rule out an acoustic neuroma').

13.3.3.7 Disability at presentation

When adults with the above types of presentation are subdivided according to their disability rating on the modified Rankin scale (rated by the research fellow from the case notes), there are clear differences (Figure 47, page 272). Those who presented with epilepsy, focal neurological deficits or symptoms unrelated to the brain AVM were not dependent. However, of those presenting with haemorrhage, three-quarters were either dead or dependent at the time, with the level of dependency being fairly evenly spread across Rankin grades 3-5. Although there was a tendency towards a less disabling presentation amongst those with SAH, in comparison with other modes of haemorrhage, numbers were insufficient to discern any statistically significant differences.

13.3.3.8 Retrospective events

Of the whole cohort, 23 (25%) had had one or more event(s) prior to presentation that could have led to earlier brain AVM diagnosis (Table 24, page 269).

Half of the adults with seizure(s) at presentation had had a prior event, and most of these were one or more seizure(s). But 8% of them had had a haemorrhage for which investigations had not revealed a cause, and 8% had had a FND that – in retrospect – was very likely to have been caused by the AVM (e.g. a rapidly-improving hemiparesis that was not investigated and labelled as functional).

One quarter of adults whose brain AVM was an incidental discovery had had prior events. These were mostly haemorrhages (21%), but a fair number had had seizure(s) (16%). Two of the three patients detected incidentally at autopsy had had retrospective events attributable to the AVM.

A minority of adults presenting with haemorrhage had had prior events, none of which were bleeds.

13.4 Summary

- The 92 adults with definite brain AVMs in the 1999-2000 SIVMS brain AVM cohort, of whom 53% were male, had a median age of 45 (range 16 to 81) years at presentation
- 19 (21%) of the cohort had their brain AVM discovered incidentally (3 at post mortem and 16 on brain/vascular imaging), one quarter of these adults had prior symptoms that were probably attributable to the brain AVM, and they were significantly older than those with symptomatic brain AVMs
- Of the symptomatic adults, 59% suffered ICrH, 34% had one or more seizures and 7% presented with a FND
- Of the adults presenting with ICrH, half of the bleeds were pure ICeH, pure SAH was always deemed to be due to associated an aneurysm rather than the brain AVM, and three quarters of all adults presenting with ICrH were dead or disabled (Rankin ≥ 3)
- 44% of the seizures at presentation appeared to be generalised without focal onset, from their description in case notes

13.5 Discussion

13.5.1 *Characteristics of presentation*

In this population-based study I have found that 21% (95%CI 14% to 30%) of brain AVMs are incidental discoveries, confirming my hypothesis that SIVMS would detect a larger proportion than in most hospital-based studies. Adults detected incidentally are significantly older than people presenting in other ways. This may, in part, be explained by 26% (95%CI 12% to 49%) of them having symptoms prior to presentation that might have led to earlier detection (Table 24, page 269).

These missed opportunities to detect brain AVMs earlier have several explanations. In part, they reflect the availability and uptake of brain imaging in the 2-3 decades prior to

the start of SIVMS. They also reflect the tendency to investigate seizures only if they have a focal onset, or if they become recurrent. Furthermore, the four adults that SIVMS could not classify as definite, but were likely to have an underlying AVM (13.3.1, page 257), illustrate how brain AVMs may not be pursued in some clinical contexts, and how they may defy detection despite best investigation. When and if these cases become definite, because clinical progression dictates further investigation, their presenting events may in some ways be 'retrospective events'.

Those incidental discoveries without prior symptoms reflect current investigation practice. For example, the vogue for imaging patients with an asymmetrical sensorineural hearing loss must surely result in more incidental discoveries (of any type, but just AVMs) than the acoustic neuromas sought?

It is also possible that these older, asymptomatic patients harbour brain AVMs with an unusually benign clinical course; they tend not to have IADSA or interventional treatment, complicating exploration of whether their angioarchitecture is in some way unique, yet providing an ideal opportunity to observe their untreated clinical course.

It was unsurprising to find that the vast majority of haemorrhages were intraparenchymal with or without extension into neighbouring ventricles or the subarachnoid space (Table 23, page 268), nor was it surprising to find that haemorrhage was the most disabling mode of presentation (Figure 47, page 272). It was interesting that seizures due to the brain AVM were apparently generalised without focal onset in 44% and in the rest had a focal onset with or without secondary generalisation.

13.5.2 *Comparison with other studies*

The Mayo clinic study offers the main opportunity for comparison with another population-based cohort [Brown, Jr. *et al.* 1996b], whilst a synthesis of data from three tertiary/quaternary referral centre databases (Toronto, New York and Paris) is perhaps the best hospital-based comparator [Hofmeister *et al.* 2000].

13.5.2.1 Other population-based studies

Compared to the Mayo clinic population-based study [Brown, Jr. *et al.* 1996b], in SIVMS presentation was more frequently incidental (21% versus 15%), less frequently haemorrhagic (47% versus 65%), and more adults presented with epilepsy (27% versus 19%). Precision in both studies is insufficient to regard these differences as significant. Furthermore, the Mayo clinic study did not separately identify presentations with FNDs making comparison difficult. If the differences between the studies are real however, they may reflect modern investigation practices, tending towards more incidental discoveries, and to identify more lesions responsible for seizure disorders, perhaps leading to AVM detection prior to haemorrhage.

13.5.2.2 Hospital-based studies

Because the synthesis of three hospital-based studies was not restricted to adults [Hofmeister *et al.* 2000], it is not surprising that at presentation their overall mean age (31 years) was lower than SIVMS median age (45 years). Women were slightly under-represented in both SIVMS (47%) and the hospital-based studies (45%), for no apparent reason. Unfortunately, it is difficult to compare mode of presentation with SIVMS, because the authors quantified total symptom burden, not a single allocated mode of presentation in each case. However, haemorrhage occurred in a similar proportion of cases (47% in SIVMS versus 53% in the hospital-based studies).

The only hospital-based study to have assessed disability of haemorrhage was an analysis of 115 incident haemorrhages, a small proportion of the Columbia AVM database cohort [Hartmann *et al.* 1998]. Interestingly, they found the distribution of these haemorrhages to be somewhat different from SIVMS (Table 23, page 268): there were more subarachnoid bleeds (30% versus 12%), fewer intraparenchymal bleeds (23% versus 46%), many more pure intraventricular bleeds (16% versus none), and fewer bleeds in combined locations (31% versus 42%). However, the Columbia paper had concluded that haemorrhage from AVMs was rarely disabling, but SIVMS provides a dramatic contrast. At presentation, 47% of the Columbia cohort had no neurological deficit (allocated Rankin grade=0), but no person with haemorrhage in SIVMS was without symptoms (which is the correct interpretation of Rankin grade 0). SIVMS found

fewer patients to be Rankin grade 1 (9% versus 37%), more patients to be Rankin grade 2-3 (39% versus 13%), and vastly more to be Rankin grade 4-6 (51% versus 3%).

There are likely to be significant differences in mode of presentation between population-based and hospital-based studies, if an individual patient data analysis were to be conducted, as there were between hospital based studies for age, sex, and proportion with haemorrhage [Hofmeister *et al.* 2000]. These differences are likely to be attributable, primarily, to the selection bias of tertiary/quaternary referral centre studies; as I have shown for presentation with haemorrhage, the most disabled patients will not be referred on for specialist management. Undoubtedly referral patterns, the particular treatment interests and availabilities of certain centres, and the definitions they use for clinical events and radiological features (Chapter 10) all contribute to the heterogeneity observed, and further reinforce the importance of complete, population-based studies.

13.5.3 *Limitations of this study*

Although SIVMS can congratulate itself for achieving population-based, unbiased ascertainment, it has failings. The availability of only two years of data at the time of writing this thesis has meant that precision is poor, with uncomfortably large 95% CIs (for example, Table 22, page 267). This will improve once the study radiologists have reviewed all the diagnostic imaging. There are clear limitations of case note review determining mode and disability of presentation. Whilst I would have liked to assess these patients myself (92 would have been feasible over 2 years), the inevitable delay from presentation to notification made this an impossibility, as did the geographical remoteness of some areas of Scotland. Relying on case note review and what happens in everyday clinical practice (often outside neuroscience centres) meant that brain imaging which was of the wrong type or conducted at the wrong time complicated allocation of presentation type, and blurred the distinction between haemorrhage and FNDs. However, my experience of reviewing case notes has reinforced my belief (perhaps a pre-existing prejudice and competing interest!) that a neurological opinion is needed for correctly identifying asymptomatic cases, seizure types, and classifying FNDs as a unique entity (rather than a repository for poorly understood presentations).

Table 22 Mode of presentation of 92 incident adults with a definite brain AVM

FND = focal neurological deficit

Mode of presentation	n (%)	n (%)	95%CI	n (%)	95%CI
		of all presentations		of symptomatic presentations	
Incidental	19 (21%)	19	(21%, 14% to 30%)	-	
Symptomatic	73 (79%)	-		-	
Haemorrhage	-	43	(47%, 37% to 57%)	43	(59%, 47% to 70%)
Epilepsy	-	25	(27%, 19% to 37%)	25	(34%, 24% to 46%)
FND	-	5	(5%, 2% to 12%)	5	(7%, 3% to 15%)
Total	92 (100%)	92	(100%)	73	(100%)

Table 23 Characteristics of the 43 adults presenting with haemorrhage from a brain AVM

Type of presenting haemorrhage	n (%)	n (%) due to aneurysm	n (%) with aneurysm(s)
Intraparenchymal	20 (46)	0	2 (20)
Intraparenchymal & intraventricular	11 (26)	0	1 (10)
Subarachnoid	5 (12)	5 (100)	5 (50)
Intraparenchymal & intraventricular & subarachnoid	4 (9)	0	2 (20)
Intraparenchymal & subarachnoid	2 (5)	0	0
Intraventricular & subarachnoid	1 (2)	0	0
Intraventricular	0	0	0
Subdural	0	-	-
Unknown	0	-	-
Total (%)	43 (100)	5 (100)	10 (100)

Table 24 Haemorrhage, epilepsy and focal neurological deficits recorded in the case notes *prior* to presentation in the 1999-2000 brain AVM cohort

FND = focal neurological deficit

Retrospective event	Type of presentation			
	Incidental (n=19)	Haemorrhage (n=43)	Seizure(s) (n=25)	FND (n=5)
Haemorrhage	4 (21%)	0	2 (8%)	0
FND	1 (5%)	1 (2%)	2 (8%)	0
Seizure(s)	3 (16%)	4 (9%)	9 (36%)	0
Any type of event	5 (26%)	5 (12%)	13 (52%)	0

Figure 45 Illustrations of imaging of included, but not definite, brain AVMs

A and B: Axial (A) and coronal (B) MRI of a possible AVM in the left pons (arrows)

C and D: Sagittal T2-weighted MRI (C) reveals high signal in the cingulate gyrus and corpus callosum (arrow), but the callosal abnormality (arrow) on left carotid angiography (D) can only be declared a possible AVM

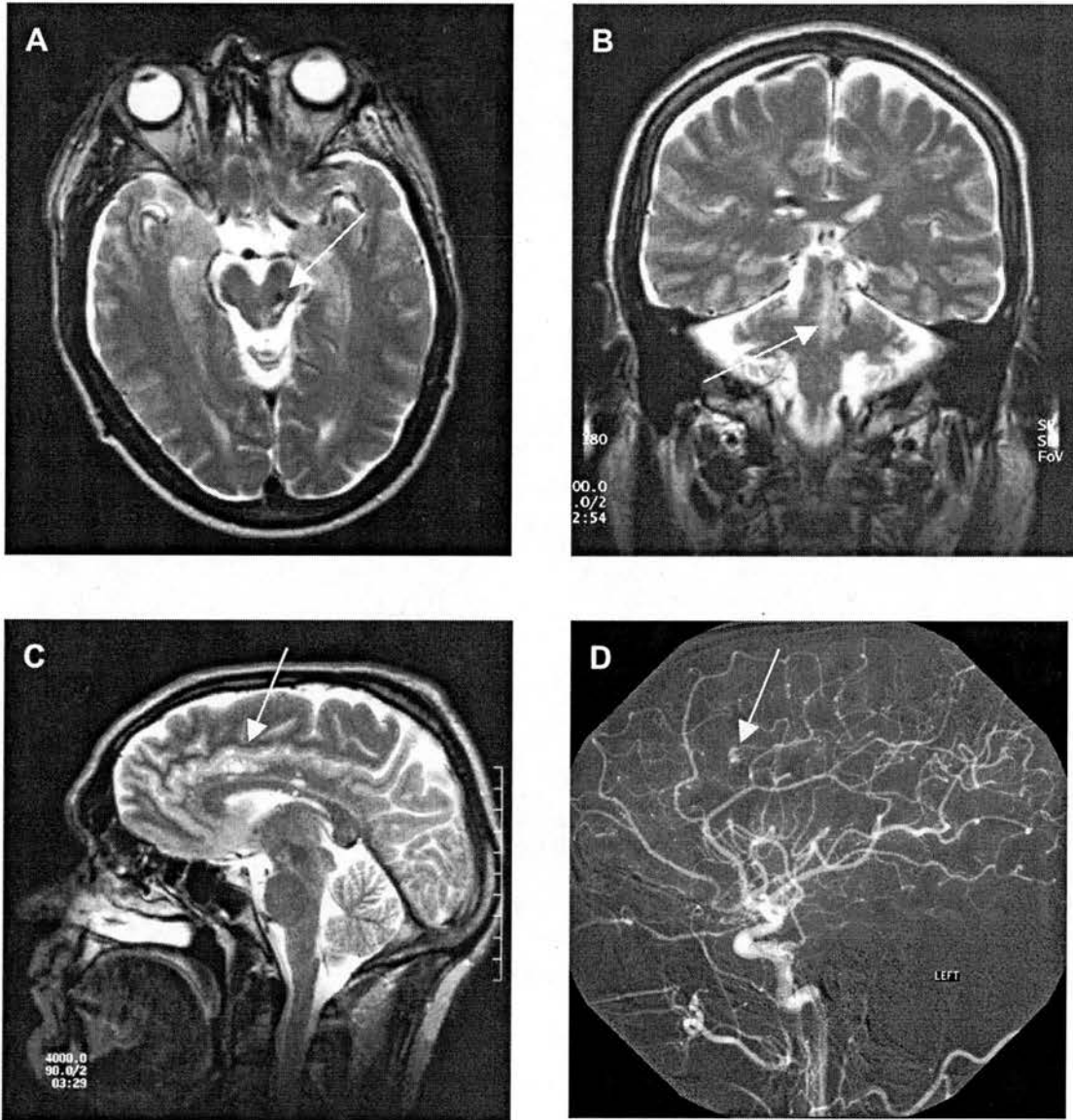


Figure 46 Illustrations of imaging of included, but not definite, brain AVMs

A and B: Axial T2-weighted MRI (A) and T1-weighted MRI with contrast (B) reveal a possible right pontine AVM with evidence of prior infarction

C and D: Axial CT (C) demonstrates a left temporal intracerebral haematoma (arrow), but catheter angiography 6 months later (D) revealed a diffuse capillary blush only (arrow)

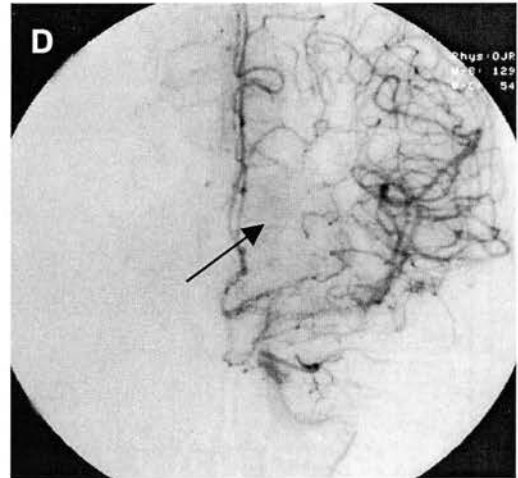
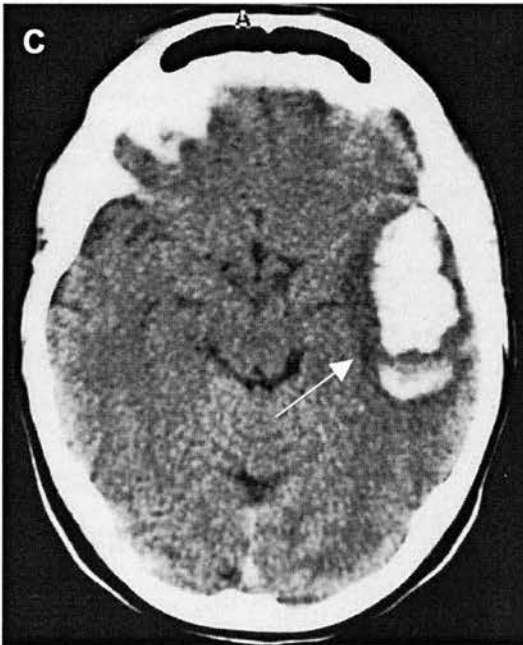
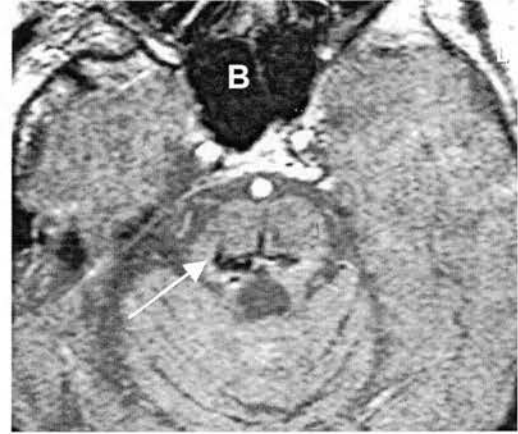
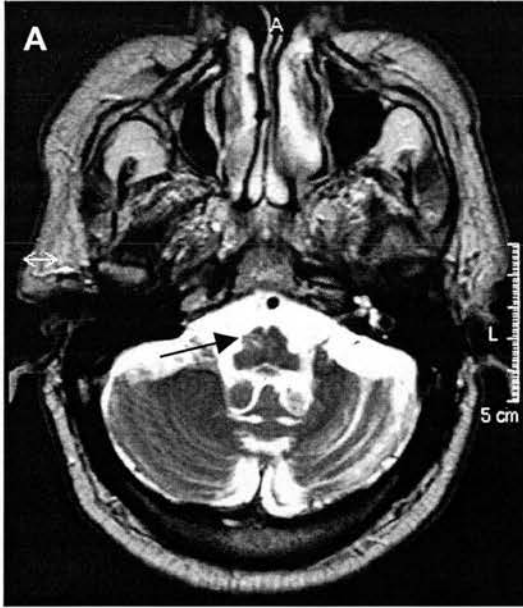
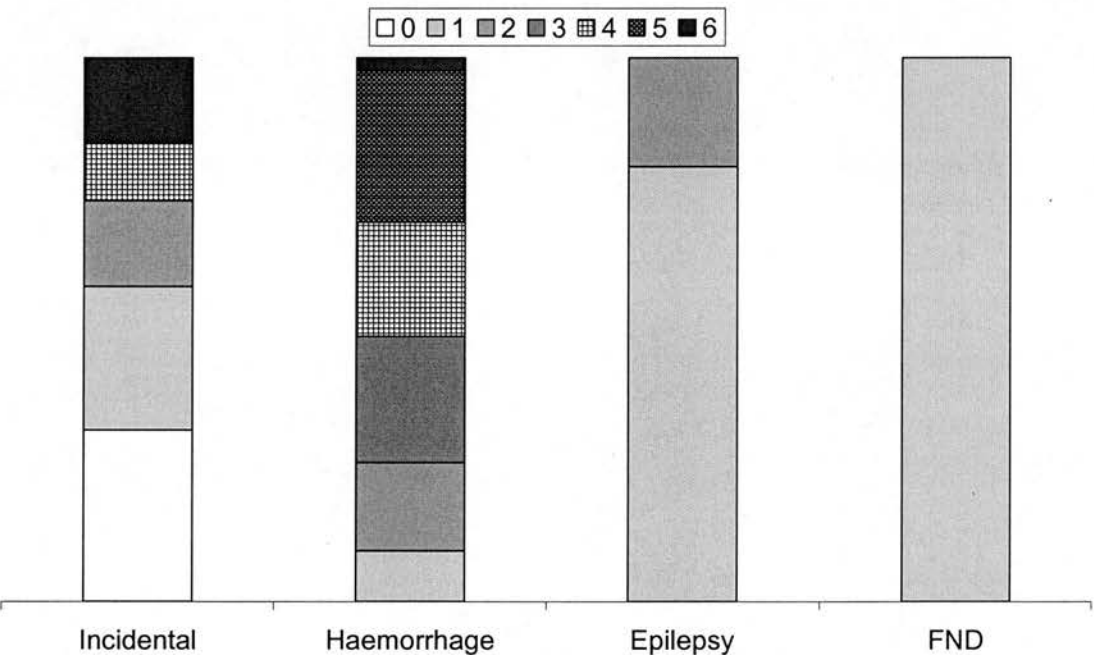


Figure 47 Distribution of the modified Rankin scale immediately following presentation, according to presentation type

Modified Rankin scale: 0 = no symptoms; 1 = minor symptoms, which do not interfere with lifestyle; 2 = some restrictions to lifestyle, but look after themselves; 3 = significant restriction to lifestyle, preventing total independence; 4 = severe handicap preventing independent existence, but not requiring constant attention; 5 = severe handicap, totally dependent, requiring attention night and day; 6 = the patient is dead.



Rankin grade	Presentation type			
	Incidental	Haemorrhage	Epilepsy	FND
0	6	0	0	0
1	5	4	20	5
2	3	7	5	0
3	0	10	0	0
4	2	9	0	0
5	0	12	0	0
6	3	1	0	0
<3 *	14 (74%)	11 (26%)	25 (100%)	5 (100%)
≥3 *	5 (26%)	32 (74%)	0	0

* p<0.05 (Fisher's exact test)

**Chapter 14. The Scottish Intracranial Vascular Malformation Study
(SIVMS) – radiological features of arteriovenous
malformations of the brain**

Chapter contents

- 14.1 Introduction
- 14.2 Methods
- 14.3 Results
 - 14.3.1 General morphological attributes
 - 14.3.2 Nidus size
 - 14.3.3 Angiographic features
 - 14.3.4 Spetzler-Martin grade
- 14.4 Summary
- 14.5 Discussion

14.1 Introduction

From my systematic review (Chapter 2), I was aware of the interest shown in angioarchitecture as a means of understanding AVM haemodynamics as well as predicting AVMs' haemorrhagic tendency (although these latter studies were based on a flawed retrospective association of angioarchitecture with prior haemorrhagic presentation). When designing SIVMS I therefore sought to collect these various attributes, with a view to exploring whether they really are predictors of subsequent prognosis. After starting data collection, I soon realised how these attributes were dependent on viewing the entire angiographic run and how observers were not consistent in their assessment, which led me to develop SIVMS definitions (Chapter 6) and quantify observer agreement (Chapter 10). Despite the time-consuming exercise of collecting these variables, they were inevitably incomplete because only three-quarters of the cohort ever had IADSA, and furthermore the quality of these data was poor (Chapter 7). This chapter briefly summarises the characteristics of the brain AVMs in the cohort.

14.2 Methods

Data were collected on paper forms, using standard definitions. Rudimentary morphological data were obtained from pathology reports if no imaging was performed; these data comprised location at least, and details about aneurysms and size if provided. If CT, MRI and IADSA were performed prior to treatment, I collected data from them all. If patients had more than one CT, MRI or IADSA, the data summarised below are from the earliest imaging study of each type that identified the AVM.

14.3 Results

14.3.1 *General morphological attributes*

Table 25 (page 279) summarises the attributes of the 92 adults with definite brain AVMs. There were no multiple AVMs, but one co-existed with a remote calcified lesion, thought probably to be a cavernous malformation (MRI was never performed). There was a tendency towards more AVMs on the right side of the brain, but 95% CIs were wide. The vast majority of AVMs were lobar in the cerebral hemispheres, and almost two-thirds of them were in 'eloquent' locations.

14.3.2 *Nidus size*

Nidus size measurements were available for 81 (88%) of adults from at least one imaging modality, or pathological examination. Pure arteriovenous fistulae were allocated a nidus size of 0mm in all directions. Maximum nidus dimension was 60mm, and the median dimension was ≤ 20 mm in all planes (Table 25, page 279). Comparing imaging modalities, there were no overall differences in average nidus size in any plane (Figure 48, page 280). Comparing measurements of the same nidus made by any two modalities, there appeared to be greater agreement between axial imaging (Figure 49, page 281) than there was when comparing IADSA with CT (Figure 50, page 282), or MRI (Figure 51, page 283).

14.3.3 *Angiographic features*

Although almost three quarters of the cohort had IADSA, the proportion investigated with IADSA varied according to the mode of presentation. The numbers investigated with IADSA, by mode of presentation, were: 8 of 19 incidental (42%, 95%CI 26% to 61%), 37 of 43 haemorrhagic (86%, 95%CI 75% to 93%), 24 of 25 seizure(s) (96%, 95%CI 84% to 99%), and 2 of 5 FND (40%, 95%CI 14% to 73%).

Aneurysms co-existed with the AVM in 20 (22%) of the cohort overall. Aneurysms were nidus in 6 (30%), remote in 4 (20%), and distal feeding artery in 3 (15%); the only aneurysms that were multiple were located on proximal feeding arteries, and these affected 11 (55%) of those with aneurysms.

Arterial feeders were most commonly multiple, as were draining veins. Arterial tortuosity, angiopathy, collateral supply and angiogenesis affected few patients. The nidus border was compact in the majority of cases. Venous varices and ectasia were not uncommon, although venous stenosis was poorly documented and rarely present.

14.3.4 *Spetzler-Martin grade*

The number of brain AVMs with a Spetzler-Martin grade simply reflects the number who had IADSA in order to define the pattern of venous drainage. The distribution of grades reflects the characteristics of those AVMs that in clinical practice were deemed suitable for IADSA (often with the intention to intervene): largely small AVMs with superficial venous drainage.

14.4 **Summary**

- Overall there was no preponderance for brain AVMs to be on one side of the brain
- 75% of AVM nidi were lobar in location, 53% were superficial, and 59% were located in surgically 'eloquent' brain areas
- Median nidus diameter was ≤ 20 mm in all dimensions
- The completeness of SIVMS's description of brain AVM morphological characteristics depends on the extent of their investigation, with angioarchitecture only available in 68 (74%) cases
- 22% of AVMs had associated aneurysms, 9% of AVMs were pure AVFs, venous drainage was purely superficial in 75%, and the majority had ≥ 2 feeding arteries and ≥ 2 draining veins

- Many angioarchitectural features (e.g. arterial angiopathy, angiogenesis, collaterals, and venous stenosis) were only present in a minority of brain AVMs

14.5 Discussion

I have found that it is possible to describe basic morphological data for a population-based cohort of adults with brain AVMs in every case, but that angioarchitecture can only be described in ~75% and even then data quality is poor (because collection of some of these variables was incomplete). This will bias any future prognosis analyses by using a subgroup of the cohort, and one that is likely to reflect a more benign clinical course, because they have survived to undergo IADSA and – often – subsequent treatment. Deep venous drainage is emerging as an independent risk factor for future haemorrhage occurrence in recent hospital-based cohort studies [Mast *et al.* 1997; Stefani *et al.* 2002], so this prognostic factor can only be tested in three-quarters of the SIVMS cohort.

Furthermore, I have found that in routine clinical practice (without the use of angiographic sizing markers and magnification correction factors), agreement between CT and MRI tends to be a little better than that between IADSA and one of the axial imaging modalities. This reinforces the superiority of axial studies for measuring nidus size.

From a comparison of three tertiary/quaternary referral centre AVM databases, there were clear differences between centres in AVM size and eloquence of its brain location [Hofmeister *et al.* 2000]. In SIVMS, 45 of 81 (56%, 95%CI 45% to 66%) cases in which nidus size was known had an overall AVM maximum diameter <3 cm in every plane, but this was only the case for 38% (95%CI 35% to 41%) in the hospital-based studies. In SIVMS, 17 of 67 (25%, 95%CI 17% to 37%) AVMs had deep venous drainage, clearly a smaller proportion than the 55% (95%CI 52% to 59%) with such drainage in hospital-based studies. Furthermore, in SIVMS AVMs were situated in eloquent regions of the brain in 59% (95%CI 49% to 68%), again a lower proportion than the 71% (95%CI 69% to 74%) in hospital-based studies. Notwithstanding the incomplete angiographic characterisation of the whole SIVMS cohort, these comparisons suggest

that the hospital-based studies were attracting larger, more complex brain AVMs, probably because of their specialist treatment capabilities, often in the 'multi-modality' treatment of larger AVMs.

These differences further emphasise the importance of studying a more representative patient group in a population-based design. Clearly, radiological evaluation that is both appropriate and comprehensive better describes the angioarchitecture of a more representative sample of adults with brain AVMs, just as a more comprehensive neurological evaluation could better characterise their mode of clinical presentation.

Table 25 Morphological features of brain AVMs on diagnostic pathological examination and/or imaging. Total n=92 unless otherwise stated

Attribute	n (%)
General AVM attributes	
Co-existent IVM?	1 (1%)*
Pure AVF?	8 (9%)
Side of the brain	Left 43%, midline 4%, right 53%
Brain area	Deep 12%, brainstem 1%, cerebellar 10%, ventricular 2%, lobar 75%
Location within brain area	Superficial 53%, corticoventricular 21%, periventricular 1%, deep 25%
Eloquent brain area?	54 (59%)
Associated aneurysms?	20 (22%)
Spetzler Martin grade (n=68)	1 (32%), 2 (40%), 3 (20%), 4 (7%), 5 (1%)
Median nidus size (n=81)	
Transverse	18mm (range 0-60mm)
Sagittal	20mm (range 0-60mm)
Vertical	15mm (range 0-50mm)
IADSA attributes	
Arterial feeders (n=66)	1 (32%), 2 (17%), 3 (8%), 4 (6%), 5 (1%), 6 (6%), 7 (1%), ≥8 (29%)
Arterial tortuosity (n=67)	None (63%), mild (28%), moderate (7%), severe (2%)
Arterial angiopathy (n=67)	None (72%), dilated (27%), dilated & stenosed (1%)
Angiogenesis (n=65)	Absent (92%), present (8%)
Collaterals (n=67)	Absent (85%), present (15%) of which 40% were dural and 60% were leptomeningeal
Nidus border	Compact (85%), diffuse (15%)
Discernible fistula in nidus (n=67)	7 (10%)
Number of draining veins (n=67)	1 (45%), 2 (25%), 3 (6%), 4 (9%), 6 (9%), ≥8 (6%)
Venous drainage pattern (n=67)	Superficial (75%), deep (12%), both (13%)
Dominant draining trunk (n=67)	52 (78%)
Venous varices (n=67)	19 (28%)
Venous ectasia (n=67)	35 (52%)
Venous stenosis (n=35)	7 (20%), of which 5 were at a dural sinus and 2 were elsewhere

* remote, probable cavernous malformation

Figure 48 Comparison of the distribution of measurements of nidus size in three directions, for brain AVMs that were visualised on CT, MRI and IADSA (n=20)

Dark lines = median dimension in mm, grey boxes = limits of 95%CI of mean, error bars = range of values, with outliers and extremes represented by circles and stars respectively

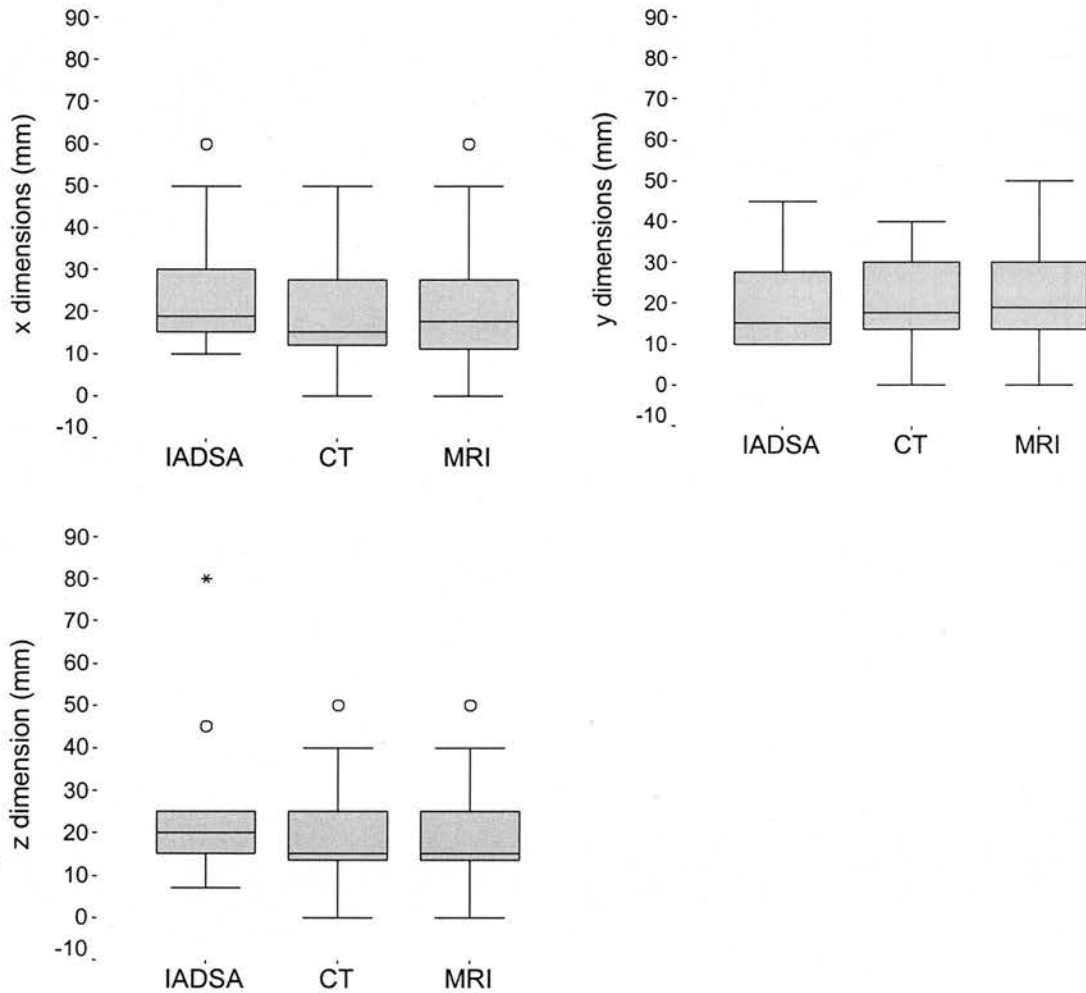


Figure 49 Bland and Altman plots comparing CT with MRI in all three planes, for brain AVMs that were visualised on both modalities (n=20)

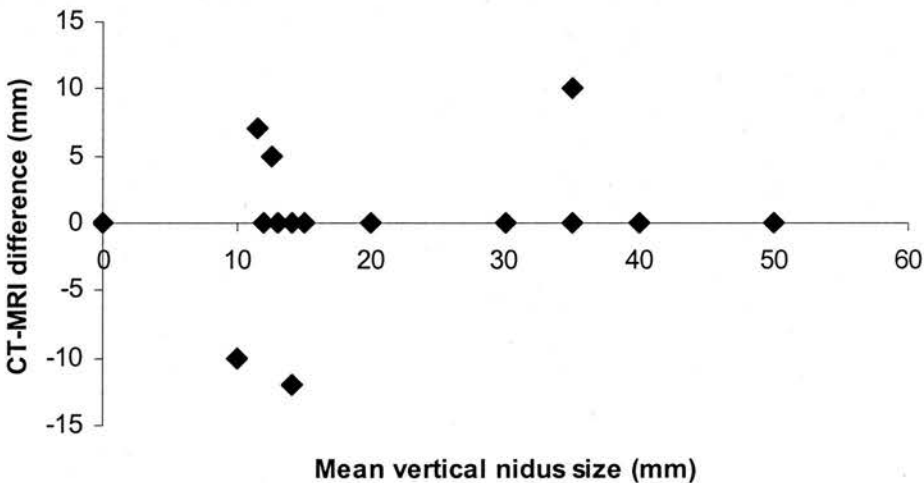
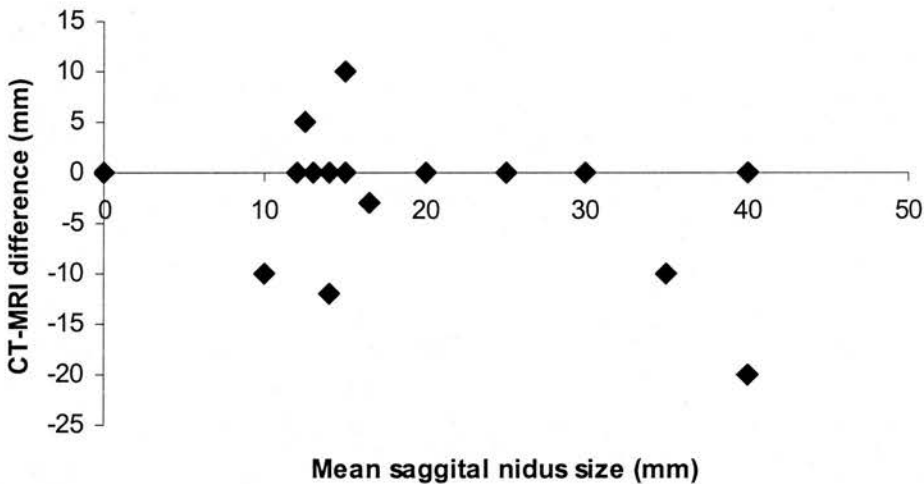
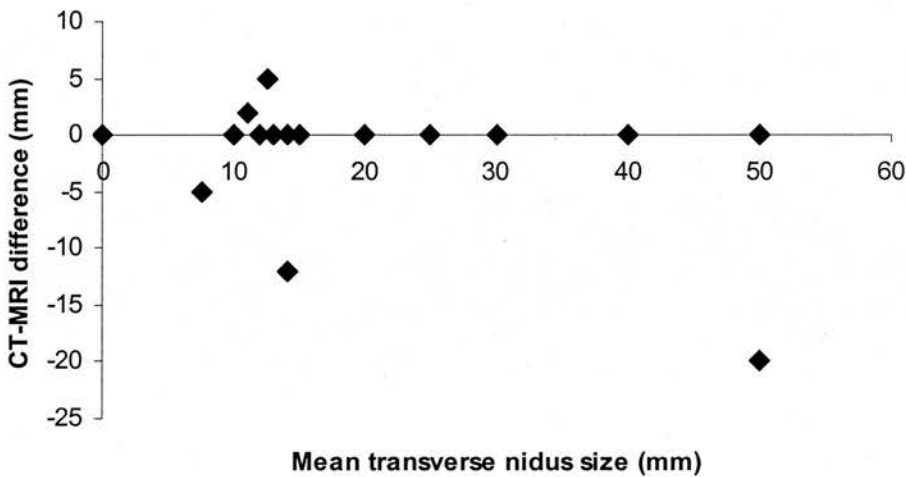


Figure 50 Bland and Altman plots comparing CT with IADSA in all three planes, for brain AVMs that were visualised on both modalities (n=20)

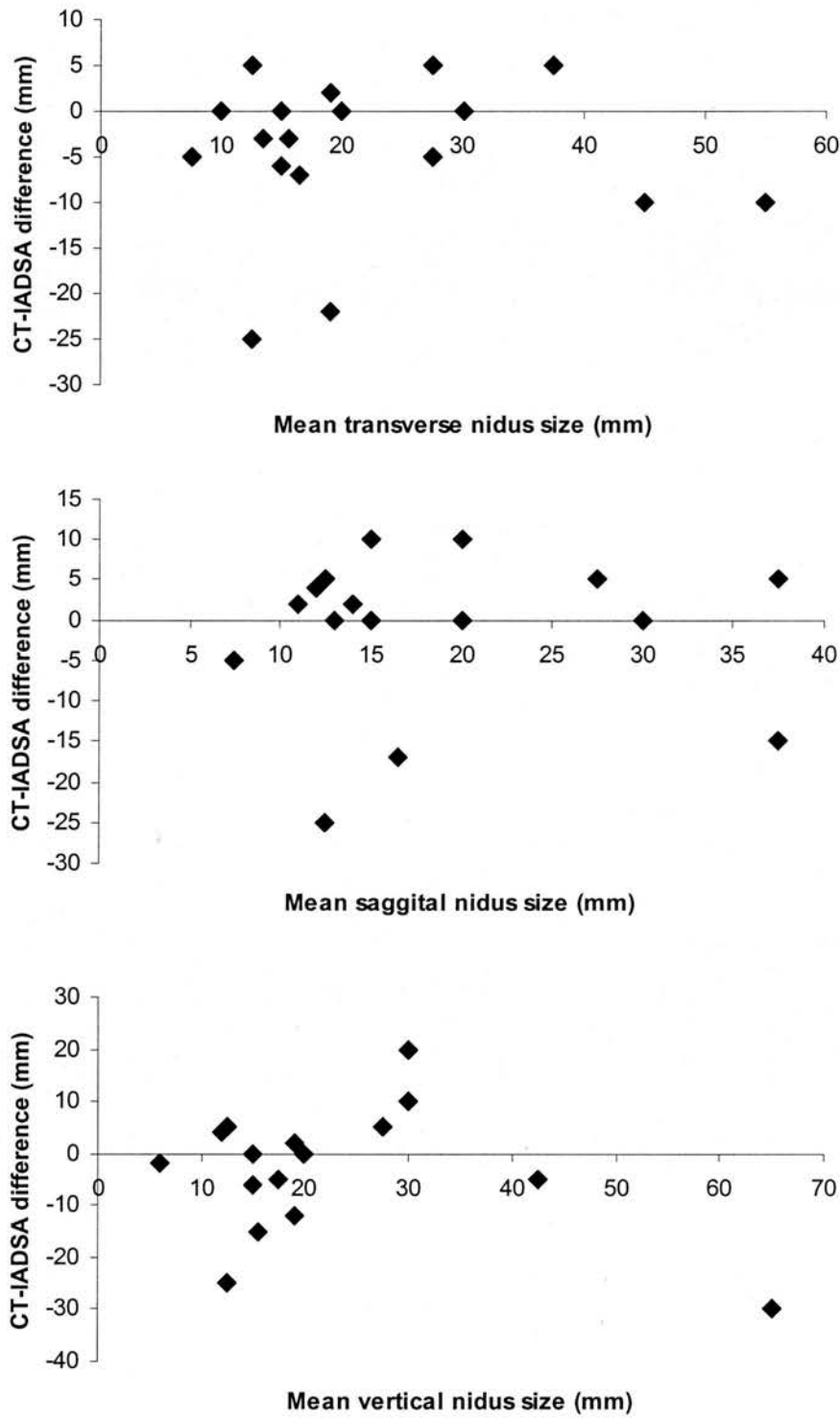
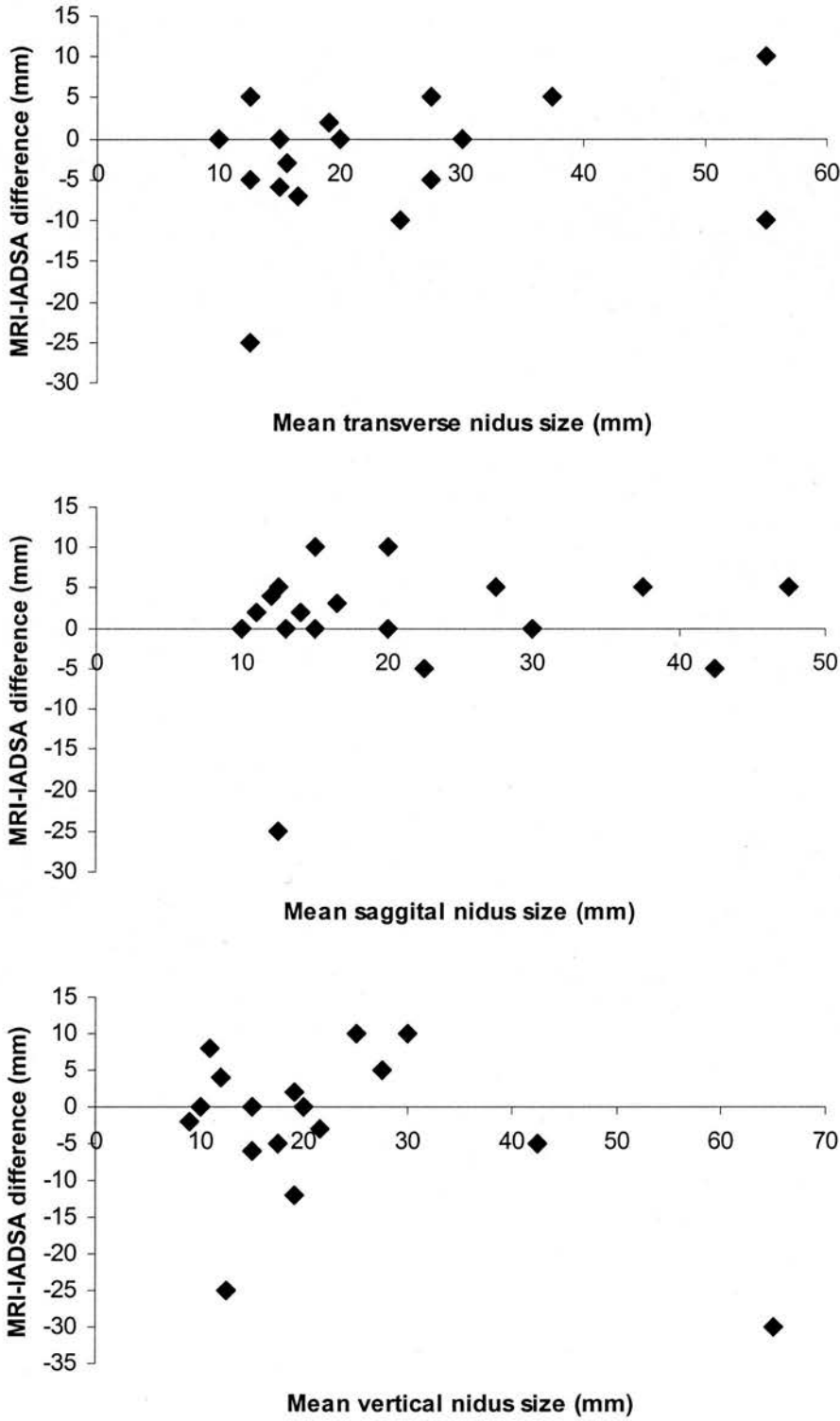


Figure 51 Bland and Altman plots comparing MRI with IADSA in all three planes, for brain AVMs that were visualised on both modalities (n=20)



Section 5: Conclusions

Chapter 15 Conclusions

Chapter 15. Conclusions

Chapter contents

- 15.1 Main findings of this thesis – a summary of summaries
- 15.2 Implications for routine practice
- 15.3 Implications for future research
 - 15.3.1 Epidemiology
 - 15.3.2 Clinical presentation
 - 15.3.3 Prognosis
 - 15.3.4 Imaging
 - 15.3.5 Aetiology
 - 15.3.6 Randomised controlled trials

15.1 Main findings of this thesis – a summary of summaries

15.1.1 *Systematic review of studies of the frequency, clinical presentation and prognosis of brain arteriovenous malformations*

- There is a serious shortage of high quality studies of the frequency, presentation, clinical course and prognosis of brain AVMs
- Whilst very little can be reliably concluded about the likely prevalence of brain AVMs, their incidence in unselected populations is of the order of 1 per 100,000 per year
- Long-term crude annual case fatality due to a brain AVM is 1-1.5%
- The crude annual risk for the first occurrence of a haemorrhage from an unruptured brain AVM is approximately 2%, and this may be increased by co-existent aneurysm(s)
- The risk of haemorrhage recurrence may be as high as 18% in the first year, although consistent risk factors for haemorrhage recurrence have not yet been observed
- Brain AVMs seem to carry an annual risk of developing *de novo* seizures of 1%, with a good prospect of control on anti-epileptic drugs
- The risk of rupture during pregnancy and for patients with HHT has not been accurately established

15.1.2 *Methods of a population-based disease register for adults with intracranial vascular malformations*

- SIVMS aspires to meet the standards of an ideal study of prognosis, as defined in Chapter 2 (Table 4, page 85)
- SIVMS includes adults who were aged ≥ 16 years at the time of a first-in-a-lifetime diagnosis of an IVM made ≥ 1 January 1999, when they were resident in Scotland

- This thesis, however, only pertains to the adults with brain AVMs, diagnosed between 1 January 1999 and 31 December 2000
- The SIVMS neuroradiologists divide brain AVM diagnoses into definite, probable and possible on the basis of diagnostic criteria
- Whilst the point of inception is the presentation that led to the brain AVM diagnosis being made, the incidence date is the year in which the definite diagnosis was first made
- Cases are recruited using multiple overlapping sources of case ascertainment (a collaborative neuroscience network, central coding of hospital discharge data and death certificates, and a mailshot to every GP in Scotland, used in the first year of SIVMS only)
- Recruitment and data collection are controlled by a Microsoft Access database, with in-built audit processes

15.1.3 *Database design for a population-based disease register for adults with intracranial vascular malformations*

- SIVMS stores paper records of study materials and identifiable data collected for every individual in the study, the fundamentals of which are stored in an electronic relational database
- A customised database application has been created using Microsoft Access, which effectively runs the study, imports data (e.g. information from secondary data sources) and exports data (e.g. for Mail Merge using Microsoft Word)
- The database is password-protected, resides on a secure network, allows multiple users to update it simultaneously, and it is regularly backed up

15.1.4 *Variables relating to patients with brain arteriovenous malformations and their clinical features*

- Data about clinical events that affect study participants are derived from their hospital and GP case notes, follow-up GP questionnaires, hospital

case notes surveillance, as well as questionnaires completed by the participants

- All clinical events that could possibly be related to a brain AVM are stored, whether they occurred at presentation (inception), prior to it (retrospective events), or during follow-up
- Clinical events are attributed to the brain AVM, an associated aneurysm, a procedure complication, another cause altogether, or unknown (when the brain AVM might have been responsible)
- The definitions used by SIVMS have external validity in the light of recent definitions proposed by the Joint Writing Group

15.1.5 *Morphological variables relating to brain arteriovenous malformations*

- SIVMS has a minimum morphological dataset for brain AVMs, specifying the location and side of the brain the nidus resides in, as well as the presence of any associated aneurysms (identified by radiological or pathological examination)
- Other attributes of the arterial feeders, nidus and draining veins are only described if brain/vascular imaging is adequate to characterise them
- Composite variables, such as the Spetzler-Martin surgical grade, may be derived if adequate data are available from pathological and/or radiological investigation
- The definitions used by SIVMS have reasonable external validity in the light of recent definitions proposed by the Joint Writing Group, the latter being more specific
- The retention of hard copies of every participant's imaging in the SIVMS library will enable *post hoc* exploration/re-categorisation of angioarchitecture

15.1.6 *The Scottish Intracranial Vascular Malformation Study (SIVMS) – data quality*

- Baseline data quality in SIVMS is a reflection of study definitions, process and database procedures
- SIVMS maximises data quality by using clear definitions of clinical and radiographic variables, automatically checking minimum data provision and consistency at data entry, deliberately analysing for errors, and spotting outliers
- 89% of patients were alive at the time of recruitment, of whom 86% were approached to join the study, of whom 69 (95%) returned their forms and consented to join SIVMS (72% of the whole cohort)
- 96% of GPs granted access to case notes, but only 91% of them have been received; 99% of consultants granted access to case notes, and 99% of these notes have been received; 98% of diagnostic scans performed at these hospitals have been received
- Basic demographic data were present for every patient, and more detailed information were available if they consented
- Complete data were available for the location of each brain AVM, but size in three dimensions was available for only 83% of the cohort

15.1.7 *The Scottish Intracranial Vascular Malformation Study (SIVMS) – evaluation of population-based design*

- The optimal sources of case ascertainment were notifications from a multidisciplinary network of collaborators in the clinical neurosciences, supplemented by routine coding of hospital discharge and death certificate data
- There was ~50% overlap between these two sources
- The cohort was domiciled in proportion to the dispersion of the Scottish population

- Age-standardised incidence ratios did not suggest significant differences in ascertainment between health board areas

15.1.8 *The Scottish Intracranial Vascular Malformation Study (SIVMS) – evaluation of ICD-10 coding and potential sources of bias*

- Coding missed 37% of adults with brain AVMs, although it benefited SIVMS by being the sole source of 4% of the whole cohort of brain AVMs
- The sensitivity of ICD-10 coding of brain AVMs was 72% (95%CI 61% to 80%); false negatives were mainly due to incorrect coding, brain AVM diagnoses not appearing on the discharge summary or death certificate, or missing records in the coding dataset
- The positive predictive value of an apparently incident ICD-10 code for a brain AVM was 46% (95%CI 38% to 55%); false positives were mainly due to intracranial aneurysms and perimesencephalic subarachnoid haemorrhage (I60.8) and other IVM types (Q28.2)
- Even with as small a cohort as 92 adults, I have also been able to demonstrate that both simplified methods of case ascertainment and reliance on IADSA for diagnosis all would have biased the cohort, sometimes very seriously

15.1.9 *Observer variation in the interpretation of catheter angiograms of brain AVMs*

- This study of 5 neuroradiologists' interpretations of 40 IADSA studies was a pragmatic effort to understand both intra- and inter-observer agreement in day-to-day assessment of AVM angioarchitecture
- The IADSAs were of adequate quality, although it will always be difficult to reflect the dynamic nature of angiography in hard copy format
- Unsurprisingly, there was greater intra-observer than inter-observer agreement

- Inter-observer agreement was greatest for characteristics such as nidus size (although there was a tendency for variation to increase as nidus size increases), moderate for Spetzler-Martin grade and the presence of aneurysms, and worst for the presence of venous stenosis and type of nidus border

15.1.10 *The point prevalence of arteriovenous malformations of the brain in the Lothian healthboard region of Scotland*

- In this first community-based study of brain AVM prevalence, I found a crude prevalence of 15 (95%CI 12 to 18) per 100,000 adults
- The prevalence may be as high as 18 (95%CI 16 to 24) per 100,000 adults if capture-recapture analysis is used to estimate the number of cases missed by my ascertainment process
- Therefore, in the year 2000, adults with a brain AVM numbered between 650-1,000 in Scotland, 7,600-11,400 in the United Kingdom and 35,400-53,000 in the USA

15.1.11 *The Scottish Intracranial Vascular Malformation Study (SIVMS) – incidence of arteriovenous malformations of the brain*

- In the years 1999 and 2000, SIVMS received 418 notifications from all sources of case ascertainment, of which 96 adults were included, and 92 had a definite brain AVM diagnosis
- The crude incidence of definite brain AVMs in Scottish adults was 1.12 (95%CI 0.90 to 1.37) per 100,000 adults per year
- The incidence of symptomatic definite brain AVMs was 0.89 (95%CI 0.70 to 1.12) per 100,000 adults per year
- The incidence of asymptomatic (incidentally discovered) brain AVMs was 0.23 (95%CI 0.14 to 0.36) per 100,000 adults per year

15.1.12 *The Scottish Intracranial Vascular Malformation Study (SIVMS)*
 – *clinical presentation of arteriovenous malformations of the brain*

- The 92 adults with definite brain AVMs in the 1999-2000 SIVMS brain AVM cohort, of whom 53% were male, had a median age of 45 (range 16 to 81) years at presentation
- 19 (21%) of the cohort had their brain AVM discovered incidentally (3 at post mortem and 16 on brain/vascular imaging), one quarter of these adults had prior symptoms that were probably attributable to the brain AVM, and they were significantly older than those with symptomatic brain AVMs
- Of the symptomatic adults, 59% suffered ICrH, 34% had one or more seizures and 7% presented with a FND
- Of the adults presenting with ICrH, half of the bleeds were pure ICeH, pure SAH was always deemed to be due to associated an aneurysm rather than the brain AVM, and three quarters of all adults presenting with ICrH were dead or disabled (Rankin ≥ 3)
- 44% of the seizures at presentation appeared to be generalised without focal onset, from their description in case notes

15.1.13 *The Scottish Intracranial Vascular Malformation Study (SIVMS)*
 – *radiological features of arteriovenous malformations of the brain*

- Overall there was no preponderance for brain AVMs to be on one side of the brain
- 75% of AVM nidi were lobar in location, 53% were superficial, and 59% were located in surgically 'eloquent' brain areas
- Median nidus diameter was ≤ 20 mm in all dimensions

- The completeness of SIVMS's description of brain AVM morphological characteristics depends on the extent of their investigation, with angioarchitecture only available in 68 (74%) cases
- 22% of AVMs had associated aneurysms, 9% of AVMs were pure AVFs, venous drainage was purely superficial in 75%, and the majority had ≥ 2 feeding arteries and ≥ 2 draining veins
- Many angioarchitectural features (e.g. arterial angiopathy, angiogenesis, collaterals, and venous stenosis) were only present in a minority of brain AVMs

15.2 Implications for routine practice

My first-ever estimates of retrospective, community-based prevalence and prospective, population-based incidence provide information for health planners about the frequency of brain AVMs, to inform the adequate provision of healthcare and resources. The dissimilarities I have observed between the composition of existing hospital-based studies and population-based studies (SIVMS and the Mayo Clinic study) urges caution in the interpretation of some of the literature. Sudden death from brain AVMs and early case fatality from AVM haemorrhage at presentation are likely to have been underestimated by hospital-based studies, as is the disability conferred by AVM haemorrhage at presentation.

The findings from the systematic review and the observer variability study also discourage reliance on most features of angioarchitecture for prognostic risk-stratification. Many of the studies suggesting that certain angioarchitectural features confer a high risk of haemorrhage are simply a retrospective correlation with prior mode of presentation, and inter-observer variation is so high in assessing most of these characteristics that the studies are unlikely to be generalisable. Although inter- and intra-observer agreement was good for nidus size, the use of size markers during IADSA is likely to improve observer agreement still further.

Whilst most of these implications are dismissive, SIVMS will ultimately make a positive contribution to clinical practice – given time – by portraying the clinical course of a representative cohort with more external validity than hospital-based studies.

15.3 Implications for future research

The existence of SIVMS, its early findings, and its likely ability to describe at least the early clinical course of its cohort has implications for the future direction of SIVMS and other research projects.

15.3.1 *Epidemiology*

In the interest of describing the global epidemiology of brain AVMs, other population-based studies – such as NYIAVMS – will provide interesting comparisons. Furthermore, continuing to monitor AVM incidence in Scotland will provide insights into whether detection rates change with increasing availability and use of brain imaging, and whether the asymptomatic detection rate declines (with better detection of earlier symptomatic events) or rises (with use of brain imaging).

15.3.2 *Clinical presentation*

It will be important to confirm the morbidity of presenting and recurrent AVM haemorrhage, which I have found to be greater than the New York group. A case-control study would help establish the role of brain AVMs in causing headache, although the knowledge of AVM diagnosis will confer a, perhaps insurmountable, recall bias. The further study of FNDs will help to establish whether AVMs do cause cerebral infarction, whether these events are simply missed bleeds, and whether they are due to steal/venous hypertension. This calls for better assessment of patients at presentation and when they experience further consequences of their brain AVM or its treatment, by neurologists with access to appropriate imaging protocols.

15.3.3 *Prognosis*

The ultimate aim for SIVMS is to establish the rates of the following primary outcomes at 5 years: survival, death or dependence (Rankin scale ≥ 3), first occurrence, and

recurrence of brain haemorrhage, development of *de novo* epilepsy, and median time to one year remission of seizures.

The extent to which I can analyse prognosis will be dependent on the frequency of outcome events. They may range from 2% to 20% per annum for the outcomes above. To increase the precision around the estimated rates of important outcomes, and increase the power of any prognostic model, SIVMS will need to recruit more patients and follow-up the whole cohort for longer to observe an adequate number of outcomes. This process would be made easier by amalgamation of the SIVMS dataset with a comparable study. However, the other groups interested in IVMs in Toronto, New York, Paris and Berlin have described considerable heterogeneity between their own hospital-based cohorts, which make them unsuitable for combination with this prospective, population-based cohort. I can only hope that the similarity I have found between SIVMS and the population-based cohort from the Mayo clinic can be reproduced if other population-based studies are set up. Amalgamation of several, similar datasets could well enhance the precision and power of prognostic data.

All outcome data in SIVMS are amenable to actuarial analysis. The critical factor in producing a reliable prognostic model using multiple regression analysis is the number of outcome events per prognostic variable. Generally a ratio of no more than 10:1 is required. Using follow-up data up to July 2004, I have observed 9 brain haemorrhages during follow-up, which would total ~25 after six years of follow-up, enabling me to design a simple prognostic model with two or three variables. More powerful models will be created for outcomes such as epilepsy and composite outcomes such as death or dependency on the Rankin scale. The prognosis for different subgroups will also be of interest (e.g. presentation with haemorrhage, pregnancy, and associated aneurysms). I will attempt to describe the first minimum spontaneous regression rate based on SIVMS.

Given that there are no randomised-controlled trials (RCTs) of the interventions for IVMs (endovascular techniques, neurosurgery and stereotactic radiotherapy), and that the current evidence base for their use rests on case series alone, observation of outcome stratified by differences in treatment in this prospective, population-based study could provide better evidence of their effectiveness. Accumulation of further data will enable independent validation of surgical grading schemes. Observation of practice

will determine whether there is geographical variation in access to and uptake of different treatment modalities.

15.3.4 *Imaging*

The most important imaging question to be addressed is what the optimal investigation for ICeH should be. An RCT could compare different modalities and timings of imaging to establish this in a large sample. The diagnostic sensitivities and specificities of the available imaging studies for identifying AVMs also need to be established in various clinical situations. Serial scanning to establish whether untreated AVMs change in size over time (and to more accurately establish the spontaneous obliteration rate) would be interesting, but it would create perhaps inappropriately high anxiety amongst participants and consequent high drop-out rates. Studying the haemodynamics of AVMs at the time of FNDs using functional imaging techniques and SPECT might help understand how these deficits come about.

15.3.5 *Aetiology*

Extremely little is known about the aetiology of AVMs, although it is likely to be multifactorial. A case-control study could address whether vascular risk factors play a part in AVM aetiology, and whether anticoagulants/antiplatelet agents play a role in AVM haemorrhage. A starting point for establishing whether there is a genetic component to apparently sporadic AVMs will be to study the family histories of a representative sample of patients (e.g. reflecting the distribution of age and modes of presentation in population-based studies).

15.3.6 *Randomised controlled trials*

All of these endeavours, especially observation and identification of particular prognostic subgroups, will create a necessary platform from which to launch RCTs. The most meaningful are likely to be comparisons of different techniques – when there is clinical equipoise about which would be best – for ruptured brain AVMs, and a policy

of no treatment against one of treatment for unruptured brain AVMs. It is heartening that, at the time of submission of this thesis, plans are afoot to apply for funding for the latter trial based in the USA and Europe.

I found setting up SIVMS far more burdensome than I had anticipated, and the final section of this thesis will be a reflection on that. As if co-ordinating multicentre, multidisciplinary collaboration and data collection was not onerous enough, simply negotiating LREC approval of an MREC-approved study was unnecessarily difficult (see next section, Chapter 16). Let alone understanding, assimilating, and debating sometimes contradictory and incompatible privacy legislation and confidentiality guidance (see next section, Chapter 17)! Although these pressures questioned my resolve at regular intervals, I rationalised my way through dark months, understanding that changes in society, a spate of public medical ‘scandals’, and Britain’s harmonisation with European directives created a unique, changing regulatory context for my observational research project. Undoubtedly, by successfully defending the ideal of unbiased research against these pressures, my bond with SIVMS became even stronger.

Section 6: A reflection on barriers to observational disease registers

Chapter 16 Ethical approval of multicentre research in Scotland

Chapter 17 Data protection legislation and confidentiality guidance

Chapter 16. Ethical approval of multicentre research in Scotland

Chapter contents

- 16.1 Introduction
- 16.2 Methods
- 16.3 Results
- 16.4 Discussion

16.1 Introduction

The foregoing original research projects would not have been possible (or funded) without the approval of the relevant ethical bodies in Scotland. This section of the thesis is a reflection on the burden that this important activity imposed on the SIVMS team. In this chapter I describe the process and outcome of ethics committee review, as it was in 1998. In the following chapter I discuss Britain's unclear and sometimes contradictory position on patients' privacy, data protection legislation, and confidentiality guidance at the time of SIVMS.

In 1991 the Department of Health delegated responsibility for ethical review of research in the NHS to Local Research Ethics Committees (LRECs) of the health authorities [Department of Health 1991]. A rapidly expanding workload [Cookson 1992], and few further guidelines, led to LRECs developing varying levels of autonomy and a diversity of working practices [Harries *et al.* 1994; Hotopf *et al.* 1995; Garfield 1995; While 1995; Redshaw *et al.* 1996; Busby and Dolk 1998]. This system posed particular problems for multicentre research at that time, which required approval from many different ethics committees [Meade 1994].

In 1997 – the year before SIVMS was set up – a long-awaited [Warnock 1988; Alberti 1995], standardised method for the review of multicentre research began with the creation of several multicentre research ethics committees (MRECs) across Britain [NHS Executive 1997]. Under this new system, multicentre research was defined as taking place over five or more LREC geographical boundaries. A multicentre application had to be submitted by its principal investigator to a single MREC somewhere in the geographical region of the study for an independent opinion on all the ethical and scientific aspects of the research proposal. Once the MREC approved the application, it must then be distributed to every LREC in the geographical location of the study. Each LREC's Executive Sub-Committee has to approve the suitability of the local site, researcher(s) and facilities before the research can start in their area.

This system was designed to minimise the burden of ethical review for LRECs and reduce the unsatisfactory delays that LRECs had caused for researchers in the past [Foster and Holley 1998]. The procedure was intended to be expedited by centralising the process of ethical review with MRECs and by providing clear guidelines to LREC

Executive Sub-Committees on what aspects of an MREC-approved multicentre application they might review and how long this should take [Palmer 1998].

The first year of the new MREC procedure was evaluated by the Research Ethics Committee Project at the Centre of Medical Law and Ethics, King's College, London [Chief Medical Officers for Scotland England and Wales 1998]; the main focus of that evaluation, however, was on the MRECs themselves. At the time of setting up SIVMS, there were no published data on the working practices of LRECs in the new era of MRECs. Therefore, following MREC approval of SIVMS in July 1998, I took the opportunity to collect data on LREC endorsement of this MREC-approved, multicentre study in the autumn of 1998 [Al-Shahi and Warlow 1999].

16.2 Methods

I had to apply to 15 LRECs for local review and endorsement of the application for SIVMS and the Lothian AVM prevalence study that had been approved by the MREC for Scotland. Each LREC application required a variable number of copies of:

- the MREC application form (23 pages)
- the supplementary form covering local investigator experience plus his or her curriculum vitae (8 pages)
- all correspondence with the MREC (6 pages)
- the research protocol, consent form and patient information leaflet (7 pages).

Recommendations for the expected timescale of LREC Executive Sub-Committee review of MREC-approved applications had been published and circulated to all LREC Chairmen and Administrators in Scotland, providing a 'reference standard' with which to compare this study's experience [Palmer 1998]. These recommendations stated that a meeting should be called within two weeks of receipt of an application and a decision should be communicated to the applicant within five working days of an LREC Sub-Committee meeting. Obtaining each LREC's opinion, therefore, should have taken three weeks.

16.3 Results

In my analysis, the date of receipt of an application by an LREC was assumed to be the next working day after its postage by first class mail; all other dates were taken from LREC correspondence. LREC identities have been anonymised.

Figure 52 (page 306) shows the delay experienced at the outset, from assumed receipt of an application to calling an LREC meeting (only eight of the 15 LRECs had established Executive Sub-Committees). The median delay to review of an application at an LREC meeting was 28 (range 14 to 97) days, twice the recommendation of two weeks.

Of particular relevance to researchers is the delay from application to final LREC approval, shown in Figure 53 (page 307); the difference between the two bars indicates the length of time taken to resolve any amendments with each LREC. The median delay from application to the time of LREC final approval was 39 (range 21 to 109) days. In fact, only three LRECs raised objections, all of which were on different grounds. One LREC disputed elements of study design (which is strictly in the jurisdiction of the MREC); the second requested additional study materials, and the third requested changes to the content of the patient information sheet.

The process of LREC application was time-consuming and labour-intensive, although I did not have to attend any LREC meetings in person and no application forms specific to any of the LRECs were requested. There was considerable variation between LRECs in the number of copies of each application they required (Figure 54, page 308). The median number of copies was 10 (range 1 to 18), amounting to a total of 5789 A4 pages, weighing 26.9kg. Photocopying and printing the applications cost £231.56 and the price of postage by Royal Mail was £77.15. The total of £308.71 does not include the cost of the salaried person-hours invested by the SIVMS secretary, a research projects' coordinator and myself.

16.4 Discussion

The original Department of Health directive to LRECs encouraged them to promote good research [Department of Health 1991]. It has been suggested that unnecessarily delaying research of potential benefit to the public is itself unethical [Stacey 1998;

Nicholl 2000]. Applicants for ethical approval of multicentre research were previously frustrated by the delays incurred by the LREC system, the costs of application, and unnecessary duplication of effort [Garfield 1995; Black *et al.* 1995; Middle *et al.* 1995; Busby and Dolk 1998; Foster and Holley 1998]. My experiences suggest that – in 1998 – Scottish LRECs were not practising uniformly, that they did not all comply with set guidelines, and although SIVMS was not delayed (because I applied in good time to accommodate potential delays), it could have been.

The creation of MRECs in 1997 was an attempt to expedite and standardise the process of gaining ethical approval for multicentre research, thereby making the process more transparent and quantifiable. In my case, delays of up to 16 weeks in gaining LREC approval, using 5789 pages of A4 paper at a cost of over £300 for materials alone have been a large price to pay for just three different LREC amendments. Comparing the 26.9kg of paperwork with an average person weighing 70kg, gaining ethical approval for multicentre research in Scotland had cost SIVMS, “more than an arm and a leg.”

By observing the practises of LRECs in Scotland, I have demonstrated that many of the old impediments still delayed multicentre research, and elimination of unnecessary variation in LREC operating procedures was still necessary to encourage timely medical research. LRECs were certainly over-burdened by a large volume of lengthy applications for approval of multicentre projects. I did not seek to address the demands imposed upon LRECs, but they were undoubtedly great.

A wealth of similar accounts from other multicentre studies in the same time period rapidly followed the submission of SIVMS's experiences for publication [Al-Shahi and Warlow 1999]. Their findings were similar to mine: not all LRECs had executive sub-committees and LRECs did not comply with their guidelines either uniformly or adequately. One involved 51 LRECs (both before and after the introduction of MRECs) in a study using cancer registry data in England, which concluded, “is it ethical for LRECs to create a bureaucratic quagmire in cases where the MREC has already given ethical approval?” [Larcombe and Mott 1999]. Another studied 125 LRECs in England after MREC introduction, found only 40% of LRECs to comply with the recommendations for handling such applications, and concluded that the system, “...at times presents an unethical barrier to potentially beneficial research” [Tully *et al.* 2000]. Another study, of 99 LRECs in England, found only 33% complied with guidance on

decision time and concluded that, "...the two tier system of ethical review retains the inefficiencies of the former system" [Lux *et al.* 2000].

This unsatisfactory situation for researchers and ethics committees alike called for further improvement to the process of ethical committee review of multicentre research.

I had some constructive solutions at the time [Al-Shahi and Warlow 1999]. Greater use of electronic communication via the internet could have reduced the cost and time delay of postage and the cost of reproduction of paper forms. LRECs required only a small proportion of the bulky MREC application form for their review; the form could have been redesigned to further minimise the amount of paperwork relayed to the LRECs. Further guidance was also needed on the extent to which observational, epidemiological research involving minimal contact with patients needed to be subject to the same process of rigorous ethical review as clinical trials of novel treatments [Royal College of Physicians 1996].

In a *BMJ* editorial following the publication of the above observational data, the president of the Royal College of Physicians of London recommended a common application form for MRECs and a shorter form for LRECs, the formation of a national advisory body, and better information and financial support for LRECs [Alberti 2000].

To the credit of those responsible for the conduct of RECs, despite researchers' protests and the recommendations of this *BMJ* editorial, plans for reform had already been laid. Their national survey of the first year of the MREC system had found there to be problems with what constituted ethical review, policy (e.g. the resolution of issues of procedure or ethics between MRECs and LRECs), and the operational system (e.g. poor dissemination to LRECs of their reviewing responsibilities and inconsistency in the amount of paperwork requested). Furthermore, the MREC central office established a working party to report on the ethical review of epidemiological and health services research, which identified 4 categories of such research (each with a different pathway of review) and recommended corresponding changes to MREC standard operating procedures.

The main reform has been the creation of the Central Office for Research Ethics Committees (COREC), responsible for policy advice, co-ordinating operational systems, training and support for RECs and researchers in the entire UK (www.corec.org.uk).

One of its first actions was to produce an operational modification for the system of ethical review of research protocols where there is no need for a local researcher, thereby minimising time and financial expenditure for both researchers conducting multicentre epidemiological research, and RECs themselves. This became effective on 1 November 2000 and will hopefully mean that, along with the other activities of COREC, my experiences with ethical approval of SIVMS will be a relic of the past. I doubt, however, that this will be the end of the story; the new operational arrangements have already been challenged as having, “an underlying emphasis on facilitating research to the extent that there is potential for it to adversely affect the interests of individual research participants” [Cave and Holm 2002], and users are bemoaning the new COREC application form [Greenhalgh 2004]!

Figure 52 Delay in days between receipt of an application and an LREC meeting

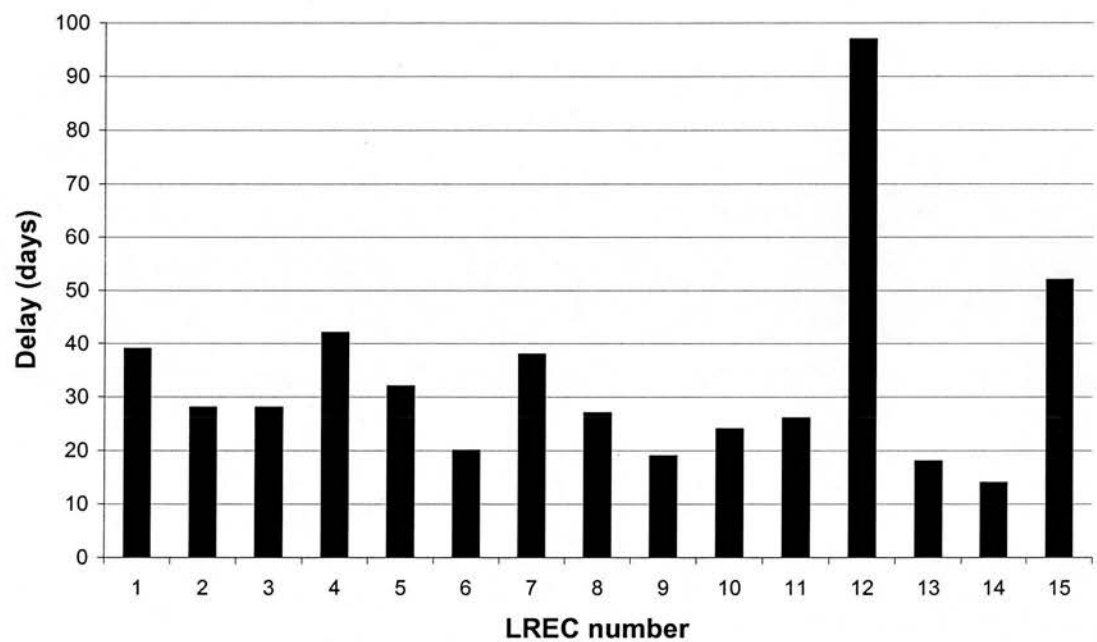


Figure 53 Delay in days between application to LREC and the initial LREC decision (light bars) and final LREC approval (dark bars)

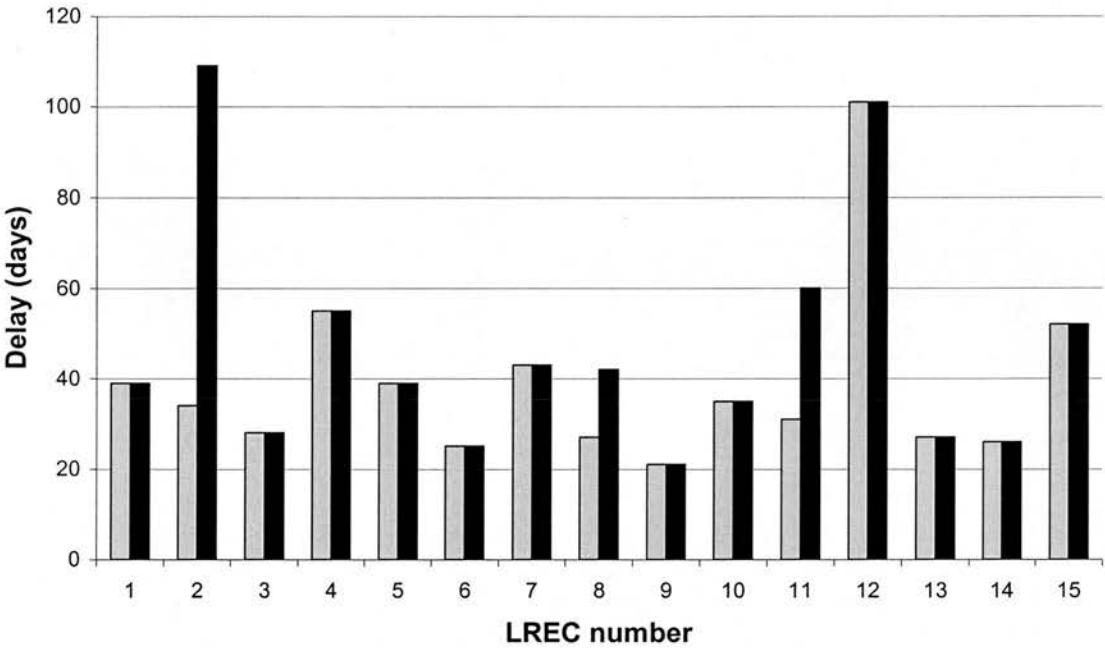
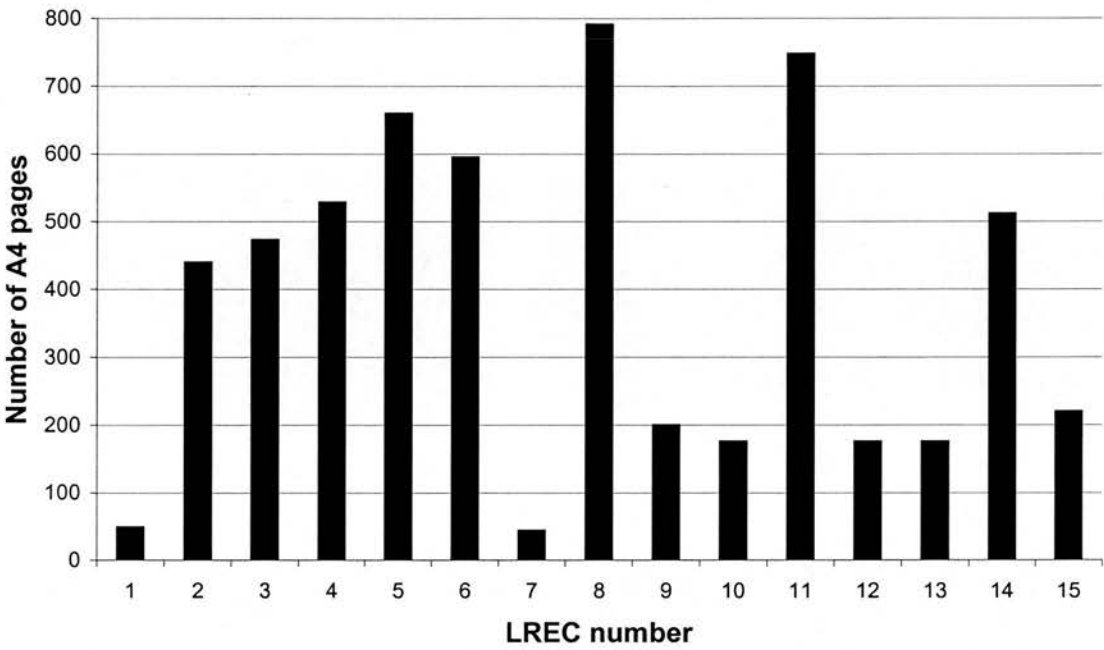


Figure 54 Number of A4 pages required for application to each LREC



Chapter 17. Data protection legislation and confidentiality guidance

Chapter contents

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- 17.3 Changes in UK data protection legislation 1999-2000
- 17.4 Changes in UK confidentiality guidance 1999-2000
- 17.5 Suggestions for resolving the contradictions in the UK in 2000
- 17.6 Changes in privacy opinion, guidance and law in the UK since 2000
- 17.7 Discussion

17.1 Introduction

Having negotiated approval of the research projects in this thesis with the MREC for Scotland and the relevant LRECs (Chapter 16), a GP who was a Medical Adviser to the local Primary Care Trust, challenged the methods of my prevalence study in late 1999 (11.2, page 228). This GP objected to my method of ascertainment, which involved asking GPs to release patient-identifiable data about adults with a brain AVM, without their explicit consent. He stated that this was ‘inviting’ GPs to breach the Data Protection Act. Similar concerns had been, and occasionally continue to be, expressed by GPs about adults in the SIVMS incident cohort study.

The data protection and confidentiality climate changed during the set-up and conduct of this thesis. In British society, the main preoccupation of the media was with a number of public inquiries into failures of care and consent in the NHS (e.g. Bristol cardiac surgery, Alder Hey retention of organs). New legislation and guidance produced in the late 1990s did not complement each other. Therefore, the wealth of new publications from different bodies landing on doctors’ doormats caused confusion. Each new piece of legislation or guidance often attracted scare-mongering publicity in the medical and national press. This compounded doctors’ anxiety, resulting in defensive attitudes towards research studies.

The challenge of defending meaningful research, yet aspiring to best confidentiality and data protection practice, diverted my attention – for months – to a detailed examination of legislation and confidentiality guidance at the time. These efforts culminated in a published letter and editorial [Warlow and Al-Shahi 2000; Al-Shahi and Warlow 2000], and further endorsement of both the incidence and prevalence study methods after negotiation – over the period of a year – with the MREC.

17.2 Background

At the dawn of the new millennium, there was still an almost unique opportunity in Britain for high quality observational epidemiology and health services research. The use of unselected and representative samples of routinely collected data from hospital and GP databases has been possible in only a few countries outside the UK. The Mayo

Clinic Foundation in Rochester, Minnesota has been a notable example of this since the early 1900s, but they were hit by privacy legislation jeopardising such research in 1997 [Melton, III 1997].

Fundamental advances in the understanding of aetiology, risk factors, and prognosis have been made through the use of population surveillance, longitudinal cohorts and case-control studies, often using disease registers [Weddell 1973; Donaldson 1992; Newton and Garner 2002]. These studies have inevitably involved using data about large numbers of people, sometimes without their explicit consent. To my knowledge, there have been no published or publicised cases where researchers or auditors conducting or contributing to such studies have been judged to breach confidentiality.

Ideally, of course, patients in any research study or audit should have given either explicit or implicit consent to the use of data that preferably should not identify them directly. Although consent is essential for most trials of any intervention, it is a somewhat utopian requirement of purely observational research and audit, particularly if it relies on huge quantities of previously collected data. But there are specific circumstances that preclude explicit consent for certain groups of patients: some individuals might be dead or untraceable, 4-14% of those with cancer deny their diagnosis [Gavin *et al.* 2002], and those with neurological diseases might well be cognitively impaired or suffer comorbid mood disorders [Carson *et al.* 2000]. Paternalism aside, approaches by researchers or auditors could cause considerable distress to such individuals. Furthermore, if a patient is approached for their consent and they do not respond, they have neither opted-in nor opted-out, leaving ambiguity about whether they should be included or not.

Systematic 'authorisation bias' invalidates the findings of observational studies if people are excluded for lack of their consent. For example, adults in Rochester, Minnesota were less likely to consent if they were female, younger than 60, living close to the Mayo Clinic and had a more sensitive diagnosis (e.g. mood disorder) [Jacobsen *et al.* 1999]. More recently, the organisers of the Registry of the Canadian Stroke Network have found that the in-hospital mortality rate was much lower for patients who gave written informed consent than for those who had not [Tu *et al.* 2004]. This is an unsurprising finding, and I have found exactly the same result with the adults in this thesis, when

comparing the all-cause mortality during follow-up of adults who gave consent to join SIVMS with those who did not (Figure 55, page 323).

If anonymised information were to be used, in an effort to protect confidentiality when using data without explicit consent, this often will not suffice. Anonymised or pseudo-anonymised identifiers can be used when searching secondary data sources for hard outcomes (e.g. death). But patient-identifiable data are clearly required to follow up patients indirectly (e.g. via GPs) for information about morbidity, and to communicate with the GP about future attempts to gain a patient's consent when it had previously not been possible to obtain it.

So, identifiable data about large numbers of people, occasionally without their consent – where it would be impossible or impractical to obtain it – is sometimes required to conduct unbiased research.

Prior to the year 2000, accessing identifiable data without patients' consent had not been highly contentious (Table 26, page 322). However, at the turn of the new millennium, rapid changes in technology, the law and society were re-shaping the way identifiable information about individuals could and should be handled. Of course, the rest of the world struggled with the same dilemmas that affected the UK. For example, in the USA, national privacy standards formed part of the Health Insurance Portability and Accountability Act (HIPAA) 1996; but an additional Privacy Rule came into effect, which permitted disclosure of information without the patient's authorisation for public health use, records research etc. [Anonymous 2001].

In Britain, there was unease. Even the disclosure of *anonymised* data – without consent from *every* individual – had been judged in a legal ruling to constitute a breach of the duty of confidence owed to patients. This might have had detrimental implications for observational research and audit [Walton *et al.* 1999], had it not been overturned by a judgement in the Court of Appeal. Lord Justice Simon Brown, in his summing up, did give a favourable opinion on the conduct of studies such as SIVMS:

“...It is clear on the information before us that for certain limited purposes patient information is used in identifiable rather than anonymised form... For present purposes, I say no more than that, provided, as I understand to be the case, the use of such identifiable data is very strictly controlled, there appears no reason to doubt that it is acceptable – whether because it falls within the public interest

defence or, as is perhaps the preferable view, because the scope of the duty of confidentiality is circumscribed to accommodate it...”

The first of the changes that destabilised doctors’ long-standing Common Law duty of confidentiality to their patients were the restrictions on processing not only electronic but also paper-based records in the Data Protection Act (DPA) 1998, which came into force on 1 March 2000.

17.3 Changes in UK data protection legislation 1999-2000

The DPA 1998, applicable throughout the UK, established a schedule of eight admirable principles, accompanied by supplementary schedules of conditions. These applied to living individuals; the deceased are not covered by DPA 1998. The second schedule requires either informed patient consent for the use of their data, or that their processing is necessary for ‘functions of a public nature exercised in the public interest’ (paragraph 5d), or ‘legitimate interests pursued by the data controller’ (paragraph 6). I believed that my research interest was legitimate, and the research was in the public interest, thereby excusing the requirement for informed consent from the patients whose GP or hospital consultant believe that direct contact with them will do them more harm than good.

Furthermore, any use of identifiable data relating to the ‘physical or mental health or condition’ of a living individual requires either their informed consent, or that the ‘processing is necessary for medical purposes’ (schedule 3, paragraph 8). Whilst these ‘medical purposes’ subsume ‘medical research’, audit is not specifically mentioned and no further definition of medical research, nor exceptions to the need for consent, are given (section 33). This is where the (deliberate, perhaps) ambiguity lies, and even more unsatisfactorily for researchers, some uses of data that would be legal under the DPA 1998 remained a breach of confidentiality under common law [Strobl *et al.* 2000]. A dilemma, perhaps, for resolution in a court of law.

However, the Data Protection (Processing of Sensitive Personal Data) Order 2000 sanctioned the processing of identifiable data so long as it was in the substantial public interest, was necessary for research purposes, did not influence decisions made about individuals, and did not damage them (paragraph 9). This too, whilst seeming supportive

of research endeavours, could be interpreted conversely; researchers were especially worried about the re-use of existing data collections because the DPA 1998 seemed to prohibit the use of information on individuals for purposes other than that originally intended [Silman and Macfarlane 2001]. Another dilemma, perhaps, for resolution in a court of law.

In the Human Rights Act (HRA) 1998 [Thomson *et al.* 2001], which came into force in October 2000, it stated, “everyone has the right to respect for his/her private life and family life, home and correspondence (article 8)... there shall be no interference by a public authority with the exercise of this right except such as is in accordance with the law and is necessary in a democratic society... for the protection of health or morals...” It is anticipated, again, that eventually judges will have to weigh the balance between the interests of the individual and those of the community [Hewson 2000].

So the law appeared sympathetic to uses of data for medical research, but left the public interest still a matter for the common law.

17.4 Changes in UK confidentiality guidance 1999-2000

In late 1999 and throughout 2000, several professional organisations responded to these legal developments by updating their guidance on confidentiality and the use of personal information (Table 26, page 322) [World Medical Association 1964; British Medical Association 1999; General Medical Council 2000; Medical Research Council 2000]. There was a real risk that strict and selective application of some directives could seriously jeopardise audit, clinical governance, and observational epidemiological research, thereby compromising patient care and the public interest.

The General Medical Council’s (GMC) guidance *Confidentiality* was perhaps the greatest cause of anxiety amongst doctors [Leslie and Webb 2001]. I think that it, like the DPA 1998, condoned a wide variety of research methods, including using patient-identifiable data without consent in certain situations. The GMC guidance did seem to lend support to the conduct of research such as SIVMS in which it is *not practicable* to obtain consent from everyone, there is no direct effect of the research on patients’ health or care, and where the benefit to future patients is far in excess of any potential harm.

Firstly, the GMC acknowledged the need for identifiable data:

Disclosure of information about patients for purposes such as epidemiology, public health safety, or the administration of health services, or for use in education or training, clinical or medical audit, or research is unlikely to have personal consequences for the patient. In these circumstances you should still obtain patients' express consent to the use of identifiable data or arrange for members of the health care team to anonymise records (see also paragraphs 16 and 18). (Paragraph 15)

However, the two paragraphs referred to above supported continued study of an unbiased cohort where it is *not practicable* to obtain consent from everyone, and where the interests of society are served by the results of research:

However, where information is needed for the purposes of the kind set out in paragraph 15, and you are satisfied that it is not practicable either to obtain express consent to disclosure, nor for a member of the health care team to anonymise records, data may be disclosed without express consent... (Paragraph 16)

In cases where you have considered all the available means of obtaining consent, but you are satisfied that it is not practicable to do so, or that patients are not competent to give consent, or exceptionally, in cases where patients withhold consent, personal information may be disclosed in the public interest where the benefits to an individual or to society of the disclosure outweigh the public and the patient's interest in keeping the information confidential. (Paragraph 18)

Lastly, the GMC's guidance invited researchers to do exactly what I did when the GP protested about the prevalence study, and request the MREC's opinion:

Where research projects depend on using identifiable information or samples, and it is not practicable to contact patients to seek their consent, this fact should be drawn to the attention of a research ethics committee so that it can consider whether the likely benefits of the research outweigh the loss of confidentiality. Disclosures may otherwise be improper, even if the recipients of the information are registered medical practitioners. The decision of a research ethics committee would be taken into account by a court if a claim for breach of confidentiality were made, but the court's judgement would be based on its own assessment of whether the public interest was served. More detailed guidance is issued by the medical royal colleges and other bodies. (Paragraph 31)

But the lack of explicit supportive statements and the ability to read the guidance two ways meant it did not compare well with the DPA 1998 [Ellis 2001]. Moreover,

researchers were left to anticipate where the public interest might be judged to lie. So the GMC's guidance *Confidentiality* led to misinterpretation, confusion and scaremongering publicity, mainly about the threat to cancer registries [Ballantyne 2000; Paterson 2001; Brewster *et al.* 2001]. Keen that cancer registries were not perceived to be the only activity jeopardised, others raised awareness about neurology research and medical research in general [Warlow 2001], health services research in general [Cassell and Young 2002], public health surveillance [Verity and Nicoll 2002], medical screening research [Wald and Law 2001], and investigating doctors' performance [Capek and Roland 2002].

17.5 Suggestions for resolving the contradictions in the UK in 2000

It seemed that selective adherence to the stricter statements in British statutory regulations and guidance could jeopardise the methodological integrity of research and audit by a blanket requirement for anonymisation of data as well as informed consent from every individual to use identifiable data about them, for each separate study. This would not just hinder the progress of medical knowledge, but might well lead to completely incorrect conclusions and make the process of clinical governance impossible, so damaging the public interest. My supervisor and I posed three solutions [Al-Shahi and Warlow 2000].

Firstly, the law needed to be clarified. The 'medical purposes' mentioned in section 33 of the DPA 1998 subsume 'medical research', but audit is not specifically mentioned and no further definition of medical research, nor exceptions to the need for consent, are given. Despite these ambiguities, a British statutory instrument (released in the same year as the DPA 1998 came into force) seemed to sanction the processing of patient-identifiable data (without mentioning informed consent) [Anonymous 2000]. Not only did these statutes need clarification, but so did the additional implications of common law and recent case law on the scope of the duty of confidentiality, and to what extent it was circumscribed to accommodate the legally-unclear public interest defence [Berg 2000].

Secondly, some *consistent* guidance offered by professional organisations would have helped. Informed consent was required for the use of identifiable information from every individual in any medical research study by the British Medical Association [British Medical Association 1999], although it was not emphatically required by other organisations [World Medical Association 1964; Royal College of Physicians 1990; Department of Health 1996; United Kingdom Central Council for Nursing 1996; General Medical Council 2000]. The requirements of audit and observational research for informed consent sometimes differed [British Medical Association 1999; General Medical Council 2000], inviting yet another unacceptable double standard in distinguishing the two [Warlow and Al-Shahi 2000].

Thirdly, unbiased public consultation is essential to determine the ideal balance between individual confidentiality and data protection on the one hand, and on the other the legitimate use – in the public interest – of patient-identifiable data without consent. Some patients may not regard their contact with the NHS as constituting implied consent to the use of identifiable data about themselves for purposes other than their own medical care. But surely there is an overriding public interest in unbiased observational research into diseases about which scant data are available, and accurate audit of medical services which may not be optimal or could be improved [General Medical Council 2000]? Hindering this progress would be unethical [Royal College of Physicians 1996].

17.6 Changes in privacy opinion, guidance and law in the UK since 2000

These three suggestions for resolution have been addressed, to varying degrees, since 2000. In Scotland and Northern Ireland, where health is a devolved matter, the evolution of the privacy struggle has differed from England and Wales.

Important new legislation in England and Wales has been incorporated into section 60 of the Health and Social Care Act (HSCA) 2001. This is intended to be an interim measure, pending improved public awareness about the uses of their data and satisfactory means of handling (preferably anonymising) data flows. Section 60 allows the Secretary of State to make regulations covering the processing of patient

information for medical purposes, where this might otherwise be subject to legal challenge under common law. Whilst the HSCA 2001 cannot be more permissive than the DPA 1998 allows, through a bureaucratic process involving a Patient Information Advisory Group (PIAG), applications for legal approval of specific projects and certain classes of research can be made, with renewal required on an annual basis.

The Confidentiality and Security Advisory Group for Scotland (CSAGS) was given the task of addressing the legal, ethical and professional requirements on confidentiality in NHS Scotland. It was set up in September 2000, as an independent committee, supported by the Scottish Executive Health Department (SEHD), “to provide advice on the confidentiality and security of health related information to the Scottish Executive, the public and health care professionals.” Approximately 150 responses to its consultative paper of July 2001 came from the health service, including the SIVMS Steering Committee. The CSAGS final report, published in April 2002, stopped short of recommending a legislative solution in Scotland. CSAGS preferred consensus, informed debate and widespread acceptance of its proposed arrangements [Fraser 2003]. It set minimum standards, including the provision of better information to patients and the universal adoption of a working practice of always questioning the need for any data collected or shared to be patient-identifiable. Although requiring a public interest defence of the use of identifiable information without explicit consent, their document states:

‘Our initial view was that explicit consent would be the requirement, based on the ethical premise that patients have a right to know about the use of their personal health data outwith their treatment needs and a right to withhold consent for such uses. That ideal remains best practice and our expectation is that it should become normal practice as better-informed patients share in future decisions about uses of their data. However, we have found the arguments in favour of permitting implied consent for [disease registers] persuasive, i.e. to safeguard valuable data for the future of services and the improvement of the health of the population.’ (paragraph 7.17)

There have been public consultation exercises about health privacy since the year 2000. A MORI poll in 2001, asking the question, “who should see my health information?” found the public favoured their GP (95%) over hospital care staff (87%) over medical research staff (63%) over other GP surgery staff (44%). Another survey, conducted by the Consumers’ Association and the NHS Information Authority (NHSIA) in 2002

(*Caring for Information, a Model for the Future*), found the public felt that *who* accessed their data was most important, not *how* the data were used, but that access should be limited to 'need-to-know' uses. This latter survey was repeated in 2003 (2,300 respondents out of 4,000 recipients i.e. 57.5% response rate); from this exercise, there evolved a 'sealed envelope' approach to patients' health data, in which patients would permit varying degrees of access to different portions of their data. I have reservations about whether these studies have made a clear enough distinction between surveying the healthy public versus patients, whether they have been representative given poor response rates, and how practical their conclusions have been.

17.7 Discussion

Ambiguous statutory regulations, contradictory guidance and a vocal minority of objecting patients or those representing them, might eventually thwart not only observational research relying on patient-identifiable data, but also audit and so clinical governance. Of course, investigators must design studies appropriately and have their use of existing, valuable data sets sanctioned. Ethics committees must adjudicate proposals consistently and should not have to endure the threat of court action to determine where the public interest lies. Patients need to be better aware of the *bona fide* purposes to which data about them may be put [Department of Health 1996].

At the moment, there are three means of secondary use of data in research. Firstly, data should be anonymised wherever possible. Of course, there are various reasons why identifiable data are needed [Black 2003]: linkage within a database, linkage between databases, adjustment for confounding factors, ensure completeness of recruitment, avoid double counting, investigate social factors, assess applicability of research findings, and directly identify individuals during follow-up. Secondly, identifiable data can be used with consent/assent. Thirdly, where neither of these approaches is possible or practicable, patient-identifiable data have to be used without explicit consent, under a public interest mandate.

What remains unclear is how the public interest impinges on the privacy interests of the individual. I believe strongly in the right to confidentiality, given the good intentions of *bona fide* researchers and their scrupulous attention to data security and safeguards to

minimise disclosure [Fienberg 2001]. I believe the public interest lies in continuing research and audit that may occasionally need to use patient-identifiable data without explicit consent. I also believe that where every citizen has a right to state-funded healthcare, they also have responsibilities to current and future patients by participation in research and audit [Doll and Peto 2001]. Final clarification may be required in case law, and some thought no doctor would be likely to seek this solution given the delay, adverse publicity and cost involved [Smith 2001]. If a researcher were to do this, “he or she would become a minor icon of 21st century medical research, for many lives and a great deal of public money would be saved” [Peto *et al.* 2004]. Sir Richard Doll has already stepped forward [Fazackerley 2004]! The alternative to a judgement in case law is further primary legislation. There are so many grey areas for medical research in the law, that a ‘Medical Research Bill’ is called for to reassure doctors, patients and the public. Others in the research community have also favoured a legislative solution [Brewster *et al.* 2001]. Although they now have one in the HSCA 2001, it is undoubtedly bureaucratic and only intended to be temporary.

Looking back, it was the GMC guidance that caused the most confusion, and others agree [Ellis 2001]. Interestingly, the GMC blamed the law; a GMC spokesman was quoted in an article as saying, “it is generally accepted now that it was not the GMC’s guidance that was at fault, it was the contradictory nature of the Data Protection Act” [Pritchard 2001]. At the time of completing this thesis, the GMC released new updated guidance (intended to be a core statement of principles, accompanied by a continually updated booklet of ‘frequently-asked questions’), but sadly their dissimilar approach to research and audit is accentuated, not diminished. This will undoubtedly make canny researchers recognise the similarity between their own endeavours and audit, doubtless culminating in a re-branding of their projects. There is already anecdotal evidence that numbers of applications to MRECs and to the ISD Privacy Advisory Committee in Scotland are dwindling. It is unclear whether this is due to research being discouraged by the regulatory environment, or research going by another name.

Thankfully SIVMS has survived – but not without a time-consuming, but worthwhile, debate with the MREC, and stopping the recruitment of venous malformations because of the difficulties this patient group caused with lack of explicit consent. Whilst SIVMS will be exempted from authorisation bias, it will also enable me to further simulate it

(Figure 55, page 323) to explore how much bias would have been introduced had consent been required in every case. Resolution of the dilemma would have been much easier if SIVMS investigators had been directly involved in the clinical care of every patient, facilitating patient consent or assent via a relative.

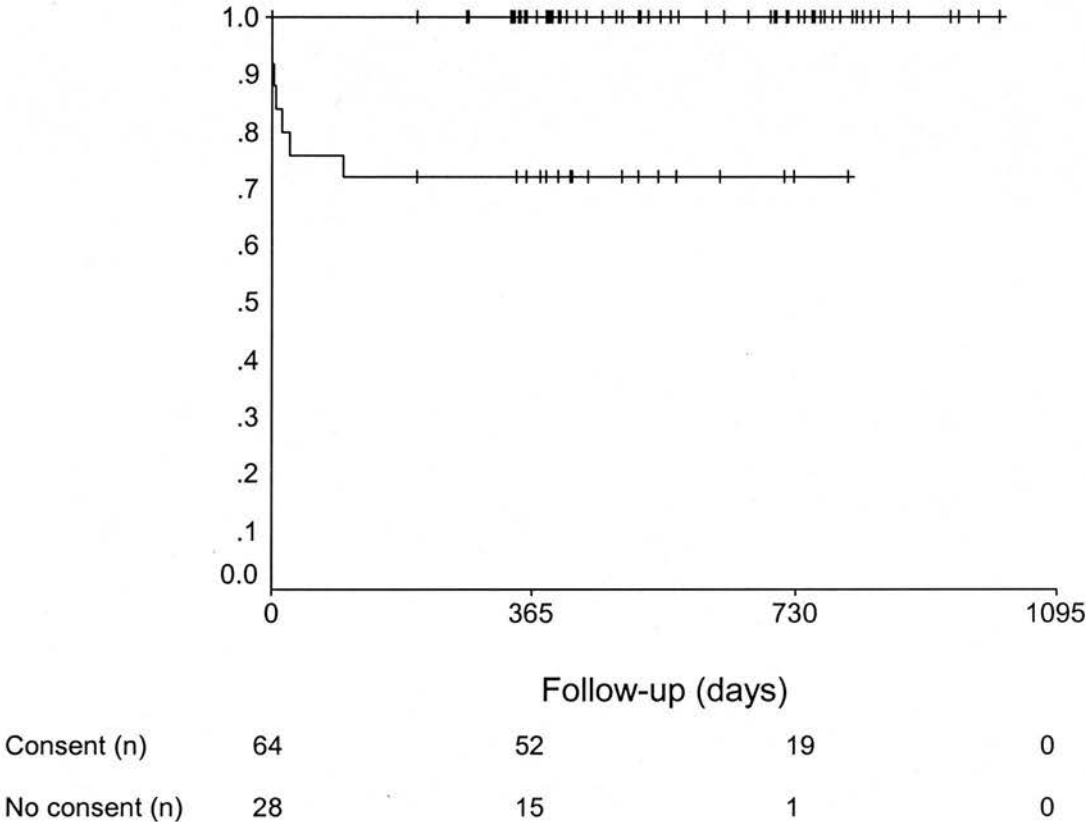
In the future, SIVMS will continue to use patient-identifiable data without informed consent (where impossible or impractical to obtain it) until challenged, using the public interest argument. Although SEHD suggested to CSAGS that it would fund a widespread public consultation and information campaign about the use of current and prior data, it remains to be seen if this will happen. If it does, it will need to be large, unbiased, and well-informed [Lawlor and Stone 2001]. Alternative forms of informed and 'community' consent [Cassell and Young 2002] may be necessary, where the public are assumed to be informed of uses of their data at any point of contact with the health service. What is certain is that, until the law is explicit, researchers will practice in a climate of uncertainty and fear [Peto *et al.* 2004].

Table 26 Statutory regulations and guidance on the use of patient-identifiable data, pertinent to medical research and audit in Britain, in reverse chronological order

Date in effect	Statutory regulations
Pending	European Convention on Human Rights and Biomedicine (1997)
2001 May	Health and Social Care Act (2001)
2000 October	United Kingdom Human Rights Act (1998)
2000 March	United Kingdom Data Protection Act (1998)
1987 August	European Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data (1981)
Date in effect	Guidance
2004 April	General Medical Council <i>Confidentiality: protecting and providing information + frequently asked questions</i>
2002 April	Confidentiality & Security Advisory Group for Scotland (CSAGS) <i>Protecting patient confidentiality</i>
2000 October	Medical Research Council <i>Personal information in medical research</i>
2000 October	World Medical Association <i>Declaration of Helsinki</i>
2000 June	General Medical Council <i>Confidentiality</i>
1999 October	British Medical Association <i>Confidentiality and disclosure of health information</i>
1997 December	Department of Health <i>Report on the review of patient-identifiable information (Caldicott report)</i>
1996 June	United Kingdom Central Council for Nursing, Midwifery and Health Visiting <i>Guidelines for professional practice</i>
1996 March	Department of Health <i>The protection and use of patient information</i>
1990 January	Royal College of Physicians of London <i>Research involving patients</i>

Figure 55 Kaplan Meier curve for all 92 adults with brain AVMs in SIVMS 1999-2000, illustrating survival free of death (all causes)

Participants are subdivided according to whether SIVMS was able to gain their consent (upper curve, n=64), or could not obtain consent (lower curve, n=28). Log rank=20.4, p<0.0001. Vertical lines indicate censoring from the analysis.



Section 7: Bibliography and appendices

Chapter 18 Bibliography

Chapter 19 Appendices

Chapter 18. Bibliography

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Chapter 19. Appendices

Steering Committee

Collaborators

Study materials

List of variables

SIVMS STEERING COMMITTEE 1999-2001

ABERDEEN

Aberdeen Royal Infirmary

Dept of Neurosurgery: Mr David Currie

DUNDEE

Ninewells Hospital

Dept of Neurology: Dr Richard Roberts

EDINBURGH

Western General Hospital

Dept of Clinical Neurosciences: Dr Rustam Al-Shahi, Dr Robin Sellar, Prof Charles Warlow

GLASGOW

Southern General Hospital

Institute of Neurological Sciences: Dr Jo Bhattacharya, Mr Vakis Papanastassiou

ABERDEEN*Aberdeen Royal Infirmary*

Dept of Forensic Pathology: Dr James HK Grieve. **Dept of Neurology:** Dr Carl Counsell, Dr Dougal McCorry, Dr John EC Hern, Dr Linda Gerrie, Dr Paul MP Crowley, Dr Richard J Coleman, Dr Kate Perkins, Dr Patrick Fox. **Dept of Neuropathology:** Dr James MacKenzie. **Dept of Neuroradiology:** Dr Alison D Murray, Dr Olive Robb. **Dept of Neurosurgery:** Mr Christopher T Blaiklock, Mr David G Currie, Mr EK Labram, Mr George F Kaar, Mr Peter C Whitfield, Ms Kirsten Elliot, Mr Marco Lee. **Stroke Unit:** Dr Roelf Dijkhuizen.

Woodend General Hospital

Dept of Medicine for the Elderly: Dr Steven Hamilton. **Dept of Radiology:** Prof Francis W Smith.

AIRDIE*Monkland District General*

Dept of Radiology: Dr Ken Wallers.

ALEXANDRIA*Lomond Healthcare NHS Trust*

Dept of Pathology: Dr Eleanor L Murray.

AYR*The Ayr Hospital*

Dept of Radiology: Dr Mark Ablett.

BRECHIN*Stracathro Hospital*

Dept of Radiology: Dr John Tainsh.

CARLISLE*Cumberland Infirmary*

Dept of Radiology: Dr P G Jennings, Dr G Athey, Dr I Khechane, Dr J Edge, Dr J Jackson, Dr R McNeill.

DUMFRIES*Dumfries & Galloway Royal Infirmary*

Dept of Radiology: Dr David Hill.

DUNDEE*Ninewells Hospital*

Dept of Neurology: Dr Duncan LW Davidson, Dr Gillian Stewart, Dr Jane Pritchard, Dr John Parratt, Dr Jonathan I O'Riordan, Dr Maria Elena Ferrugia, Dr Richard Roberts, Dr Robert J Swingler, Dr Kathleen White, Dr Pushkar Shah. **Dept of Neuropathology:** Dr Nazaar Alsanjari. **Dept of Neuroradiology:** Dr Gavin Main, Dr Graeme Houston, Dr John Tainsh. **Dept of Neurosurgery:** Dr BS Caussy, Mr D Mowle, Mr Eric S Ballantyne, Mr Nigel Page, Mr Sam Eljamel, Mr A Kumar. **Stroke Unit:** Dr Ronald S MacWalter, Ms Hazel Fraser.

DUNFERMLINE*Queen Margaret Hospital*

Dept of Radiology: Dr Hamish Ireland.

EAST KILBRIDE*Hairmyres Hospital*

Dept of Radiology: Dr F Mohsen, Dr Fiona Gardiner, Dr Samuel Millar.

EDINBURGH*Edinburgh Royal Infirmary*

Dept of Radiology: Dr Dilip Patel, Dr Graham McKillop, Dr Tom Fitzgerald.

Edinburgh University Medical School

Dept of Forensic Pathology: Prof Anthony Busuttill.

Western General Hospital

Dept of Clinical Oncology: Dr Anna Gregor, Dr Sara Erridge. **Dept of Neurology:** Dr Carlos Veira, Dr Gordon Gubitz, Dr Nic U Weir, Dr Rebecca Aylward, Dr Adam Zeman, Dr Andrea Lowman, Dr Anna Williams, Dr Belinda Weller, Dr Cathie LM Sudlow, Dr Christian J Lueck, Dr Colin J Mumford, Dr Colm Henry, Dr Jon Stone, Dr Joseph Kwan, Dr Malcolm R Macleod, Dr Martin Zeidler, Dr Peter Hand, Dr Richard Knight, Dr Richard J Davenport, Dr Robin Grant, Dr Ronan Mac Donagh, Dr Rustam Al-Shahi, Dr Sarah L Keir, Prof Bob G Will, Prof Charles P Warlow, Prof Peter AG Sandercock, Dr Will Whiteley, Dr Chris Butler, Dr Sarah Cooper, Dr Martyn Bracewell, Dr Craig Heath, Dr Ravi Malhotra. **Dept of Neuropathology:** Dr Alistair Lammie, Dr Colin Smith, Dr Stephen Wharton, Prof James Ironside, Prof Jeanne E Bell, Dr Reena Kurian. **Dept of Neurophysiology:** Dr Greg Moran, Dr Roger E Cull. **Dept of Neuroradiology:** Dr Don A Collie, Dr George T Vaughan, Dr Phil M White, Dr Robin J Sellar, Dr Rod Gibson, Prof Joanna M Wardlaw, Dr David Summers. **Dept of Neurosurgery:** Mr Michael O'Sullivan, Miss Lynn M Myles, Mr Andrew Evans, Mr Brad Hoffman, Mr Y-H Yau, Mr Henry D Atkinson, Mr Ioannis Fouyas, Mr James AW Steers, Mr Mario Delgado, Mr Patrick FX Statham, Mr Raju Sangra, Mr Rupert Price, Mr Saurabh Sinha, Mr Tew Han, Mr Thomas Russell, Mrs Anne Mitchener, Prof Ian

Whittle, Mr Jerard Ross. **MRC Molecular Medicine Centre:** Dr Mary E Porteous. **Stroke Medicine:** Prof Martin S Dennis, Dr Richard I Lindley.

ELGIN

Dr Gray's Hospital

Dept of Radiology: Dr Ken Brown.

FALKIRK

Falkirk & District Royal Infirmary

Dept of Neurology: Dr Gillian L Hall, Dr Margaret-Ann Macleod, Dr Rebecca Aylward. **Dept of Radiology:** Dr Josephine Barrie, Dr K H Jawad, Dr Raj Burgul.

GLASGOW

Gartnavel General Hospital

Dept of Radiology: Dr Ramsay Vallance.

Glasgow Royal Infirmary

Dept of Medicine for the Elderly: Dr Jacqueline Taylor. Dr Peter Langhorne, Prof David Stott, Dr Jennifer Burns. **Dept of Radiology:** Dr Allan Reid, Dr G H Roditi.

Glasgow University Medical School

Dept of Forensic Medicine: Dr Louay M Al-Alousi.

Ross Hall Hospital

Dept of Radiology: Dr David Kean.

Southern General Hospital

Dept Anaesthetics: Dr Anne Burke. **Dept of Neurology:** Dr A Myfanwy Thomas, Dr Aileen McGonigal, Dr Colin P O'Leary, Dr Donald G Grosset, Dr G Kalamangalam, Dr George Gorrie, Dr Hani Ben Amer, Dr Hugh J Willison, Dr James Overell, Dr John D Greene, Dr John P Ballantyne, Dr Keith Muir, Dr Mark McCarron, Dr Rachel Thomas, Dr Richard A Metcalfe, Dr Richard KH Petty, Dr Rod Duncan, Dr Stuart Webb, Dr Tracey Baird, Dr Ursula Schultz, Dr William F Durward, Prof Ian Bone, Prof Peter GE Kennedy, Dr Vicky Marshall. **Dept of Neuropathology:** Dr David Doyle, Dr James AR Nicoll, Prof David Graham, Dr Susan Robinson. **Dept of Neurophysiology:** Dr Alan C Mann, Dr Aline Russell, Dr Andrew Weir. **Dept of Neuroradiology:** Dr David Kean, Dr Evelyn Teasdale, Dr Jo J Bhattacharya, Dr Sarah Jenkins, Prof Donald Hadley, Dr Celestine Santosh. **Dept of Neurosurgery:** Dr Shabin Joshi, Miss Jennifer Brown, Miss Mary Murphy, Miss Patricia Littlechild, Mr J Mohan, Mr John Brecknell, Mr Kamal Goyal, Mr Kenneth Lindsay, Mr Laurence T Dunn, Mr Michael Fitzpatrick, Mr Philip Barlow, Mr Robin Johnston, Mr Vakis Papanastassiou, Mr William AS Taylor, Prof Graeme M Teasdale, Ms Claire Nicholson, Mr J. Jay, Mr A. Kay, Mr Donal Walsh.

Stobhill NHS Trust

Dept of Medicine for the Elderly: Dr Christine McAlpine, Dr Pamela Fraser. **Dept of Radiology:** Dr Ian Mcleod, Dr Rhona Stevens.

Victoria Infirmary

Dept of Medicine for the Elderly: Dr Jan Potter, Dr M A Roberts. **Dept of Radiology:** Dr Andrew Downie, Dr Ian McLaughlin, Dr J Lauder.

Western Infirmary

Dept of Medicine & Therapeutics: Prof Kennedy R Lees, Prof Martin J Brodie. **Dept of Radiology:** Dr Michael Cowan, Dr Nigel McMillan.

GREENOCK*Inverclyde Royal Hospital*

Dept of Radiology: Dr Alan Ramsay, Dr P F Walsh.

INVERNESS*Raigmore Hospital*

Dept of Medicine: Dr Frank Williams. **Dept of Radiology:** Dr A Macleod, Dr Alistair Todd, Dr David Goff, Dr David Nichols, Dr George Aitken, Dr Helen Shannon, Dr Peter Henry.

KILMARNOCK*Crosshouse Hospital*

Dept of Radiology: Dr David Rawlings, Dr Elspeth Lindsay, Dr George McLaughlin, Dr Morag McMillan, Dr Neil Corrigan, Dr Patrick Crumlish, Dr WMF Dean, Dr John Miller.

KIRKCALDY*Victoria Hospital*

Dept of Radiology: Dr Caroline Clark.

LIVINGSTON*St John's Hospital*

Dept of Radiology: Dr Ian Parker.

MELROSE*Borders General Hospital*

Dept of Medicine for the Elderly: Dr Paul Syme. **Dept of Radiology:** Dr Andrew Pearson, Dr David Hardwick, Dr Hamish McRitchie, Dr J H Reid.

NEWCASTLE UPON TYNE*Newcastle General Hospital*

Dept of Neuroradiology: Dr Anil Gholkar, Dr Calvin Soh.

PAISLEY*Royal Alexandra Hospital*

Dept of Radiology: Dr Alan Wallace.

PERTH*Perth Royal Infirmary*

Dept of Radiology: Dr Richard Murray.

STIRLING*Stirling Royal Infirmary*

Dept of Radiology: Dr Peter McDermott.

STORNOWAY*Western Isles Hospital*

Dept of Radiology: Dr Ian Riach.

WISHAW*Wishaw General Hospital*

Dept of Radiology: Dr D Alcorn, Dr John Roberts, Dr M Callaghan, Dr M El-Sayed, Dr Mustafa Fleet, Dr Susan Reid.

NOTIFICATION

1. Collaborator notification form
2. GP mailshot
3. Notification thank you (collaborator)
4. Notification thank you (GP)

EXCLUSION

5. Patient excluded (GP)
6. Patient excluded (collaborator)
7. Patient excluded (collaborator notifier)
8. Patient excluded (GP notifier)

RECRUITMENT

9. Consultant enrolment
10. Consultant (notifier) enrolment
11. Consultant enrolment (dead)
12. Consultant (notifier) enrolment (dead)
13. Consultant (not neuroscience) enrolment
14. Consultant (not neuroscience) enrolment (dead)
15. Consultant (another hospital) enrolment
16. Consultant enrolment (ISD notification)
17. GP enrolment
18. GP (notifier) enrolment

RECRUITMENT (CONTINUED)

19. GP enrolment (dead)
20. Change of GP
21. Patient enrolment
22. Patient enrolment (delayed)
23. Patient enrolled
24. Patient enrolled (dead)
25. Patient enrolled (details changed)

COLLECTION OF CASE NOTES

26. GP notes request
27. GP notes request (dead)
28. Hospital notes request
29. Hospital notes request (dead)

FOLLOW-UP

30. GP annual follow-up (no patient questionnaire)
31. GP annual follow-up (patient questionnaire)
32. Annual GP case notes request
33. Annual hospital case notes request
34. Patient annual questionnaire
35. Patient annual epilepsy questionnaire
36. Patient annual headache questionnaire

SIVMS PATIENT NOTIFICATION

1

Please insert these essential identifying details for the patient you wish to notify.

They must be Scottish residents

Forename	<input type="text"/>		
Surname	<input type="text"/>		
Date of birth	<input type="text"/> day	<input type="text"/> month	<input type="text"/> year
... or affix the patient's identification label from your hospital			
Hospital No.	<input type="text"/>	X ray/Path No.	<input type="text"/>

2

Now indicate the type of IVM the patient is diagnosed with and when the diagnosis was first made (by imaging or biopsy).

They must be first diagnosed AFTER 1/1/1999

Type(s) of IVM	Indicate the quantity:
AVM Brain arteriovenous malformation	<input type="checkbox"/>
CM Cavernous malformation	<input type="checkbox"/>
VM Venous malformation	<input type="checkbox"/>
DAVM Dural arteriovenous malformation	<input type="checkbox"/>
IIT Intermediate type	<input type="checkbox"/>
HOS Undetermined / Uncertain	<input type="checkbox"/>
Date of first diagnosis (by imaging or biopsy)	<input type="text"/> day month year

3

Please tell us which consultant and GP look after this patient.

Consultant initials & surname <input type="text"/>	GP initials & surname <input type="text"/>
Hospital name & address <input type="text"/>	Practice name & address <input type="text"/>

4

Now add your signature and today's date.

Signature <input type="text"/>
Print your name <input type="text"/>
Date <input type="text"/> day month year

5

Please post or fax us this notification form...

SIVMS Contact Dr Rusem Al-Shahi, MRC Clinical Training Fellow Miss Rosemary Anderson, SIVMS Secretary Department of Clinical Neurosciences Western General Hospital NHS Trust Crewe Road Edinburgh EH4 2XU	TELEPHONE / FACSIMILE 0131 537 2944
---	--

18 February, 2003

Dr «GP_INITS» «GP_SNAM»
 «PR_A_1»
 «PR_A_2»
 «PR_A_3»
 «PR_A_4» «PR_POSTC»

Department of Clinical Neurosciences
 Bramwell Dott Building
 Western General Hospital
 Crewe Road
 Edinburgh EH4 2XU
 tel/fax: 0131 537 2944



Dear Dr «GP_SNAM»

Patients newly-diagnosed with any type of Intracranial Vascular Malformation in 1999

We would be very grateful for your help with the Scottish Intracranial Vascular Malformation Study (SIVMS) to establish the incidence of *all* people affected by *any type* of intracranial vascular malformation (IVM) in the Scottish population. As you know, IVMS are an important cause of intracranial haemorrhage, epilepsy, headache, and progressive neurological deficit in otherwise healthy young adults.

You are not likely to have many, or even any, patients on your list with this diagnosis. However, we would be very grateful to you for taking a minute or two to list on the attached three-stage questionnaire any patients, about whom we have not already contacted you, who you know fulfil the following criteria:

➔ 1st diagnosed AFTER 1ST JANUARY 1999

➔ With any type of brain IVM:

- Arteriovenous malformation (AVM)
- Cavernous malformation/cavernoma (CM)
- Venous malformation/anomaly (VM)
- Dural arteriovenous fistula (DAVF)

➔ Age 16 years or over

SIVMS is a prospective, observational study of all patients in Scotland diagnosed with **any type** of intracranial vascular malformation (IVM) after 1st January 1999. The study is based in the departments of Neuroradiology, Neurology, Neurosurgery and Neuropathology in all four Scottish Neuroscience centres. Our collaborative network encompasses all the other Radiology Departments in the country. We aim to register **all** patients with an IVM in Scotland to better define the epidemiology of these rare, but important conditions. Data will be collected from individuals' medical records. Copies of their imaging will be stored for further analysis. **Patient confidentiality will be respected at all times. We have the approval of the Scottish Multicentre Research Ethics Committee and your Local Research Ethics Committee.** The protocol is available on request, or from our website.

Please do not bother to return the form if you do not have any suitable patients. If you would like to obtain any patient's permission for the release of this information, we enclose a letter that you could send to them for this purpose. Please let us know if you require administrative or financial assistance in approaching any of your patients who meet these inclusion criteria. Thank you very much for your help.

Yours Sincerely

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

Prof Charles P Warlow
Professor of Medical Neurology

Steering Committee

Aberdeen: Mr DG Currie, Dundee: Dr RC Roberts, Edinburgh: Dr R Al-Shahi, Dr RJ Sellar, Professor CP Warlow, Glasgow: Dr JJ Bhattacharya, Mr V Papanastassiou

Funded by the Medical Research Council and the Chief Scientist Office of the Scottish Executive Health Department

Scottish Intracranial Vascular Malformation Study

➔ FIRST diagnosed AFTER 1ST JANUARY 1999
 ➔ With any type of brain VM
 ➔ Age 16 years or over

1 Please list below any patients known to you who are...

Patient's Name (BLOCK CAPITALS please)	Diagnosis (please ✓)				Date of birth (if known)	Hospital attended (if known)
	AVM Arteriovenous malformation	CM Cavernous malformation	DAVF Dural arteriove- nous fistula	VM Venous malformation		
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		

2 Please add any comments if applicable

3 Signature

Date

day/month/year

Dr «GP_INITS» «GP_SNAME» «GMC#»

4

Please return this form to: SIVMS, Bramwell Dott Building, Department of Clinical Neurosciences, FREEMOST, Western General Hospital, Edinburgh EH4 0HX

February 2000

Dear

Re. The Scottish Intracranial Vascular Malformation Study

I wonder if you would be prepared to help Professor CP Warlow and his team of researchers at all the other Neuroscience Departments across Scotland with a study they are conducting? They are trying to find out how many people in Scotland are affected by a type of tangle of blood vessels in the head, called an intracranial vascular malformation, or 'IVM' for short. I am writing to you because I believe you have one of these IVMs, or have been affected by one in the past.

Their study has full approval from the relevant ethics committees. It involves examining your case notes to extract a few details of your medical history, and sending you a questionnaire once each year. They will ensure that any information collected about you will be confidential and used only for their study.

Could you please return the tear-off slip to me, indicating whether you are happy for me to pass on your details to Professor Warlow. If you are, he will be in touch with you himself.

Yours Sincerely,

Dr «GP_INITS» «GP_SNAM»

✂-----

	Please	✓	appropriate box
	Yes		No
<i>I am happy for Professor Warlow, or a member of his team, to examine my case notes</i>	<input type="checkbox"/>		<input type="checkbox"/>

Signature _____

Date ____ / ____ / ____

Print your name _____

My GP is Dr «GP_INITS» «GP_SNAM»
«PR_A_1»
«PR_A_2»
«PR_A_3»
«PR_A_4»
«PR_POSTC»

Department of Clinical Neurosciences
 Bramwell Dott Building
 Western General Hospital
 Crewe Road
 Edinburgh EH4 2XU
 tel/fax: 0131 537 2944
 e-mail: sivms@skull.dcn.ed.ac.uk
 web: <http://www.dcn.ed.ac.uk/ivm/>



19 February, 2003

«collName»
 «CollJobTitle»
 «Department»
 «CentreAddr1»
 «CentreAddr2»
 «CentreCity»
 «CentreRegion» «CentrePostCode»

Dear «CollTitle» «CollSurname»,

Re. «patName»
 «PatAddress1» «PatAddress2» «PatAddress3» «PatCity» «PatDistrict»
 «PatPostCode»

Thank you very much for letting us know about «PatTitle» «PatSurname»'s recent diagnosis of an intracranial vascular malformation (IVM). We will now wait four weeks before sending any study enrollment forms to his GP and hospital consultant. We enclose a blank notification form to replace the completed form you have just sent us, for the next patient you see with a new diagnosis of an IVM!

Yours Sincerely,

Dr Rustam Al-Shahi
MRC Clinical Training Fellow
 Sivms No. «PatID»

Prof. Charles P. Warlow
Professor of Medical Neurology

Department of Clinical Neurosciences
 Bramwell Dott Building
 Western General Hospital
 Crewe Road
 Edinburgh EH4 2XU
 tel/fax: 0131 537 2944
 e-mail: sivms@skull.dcn.ed.ac.uk
 web: <http://www.dcn.ed.ac.uk/ivm/>



19 February, 2003

«GPTitle» «GPName»
 «GPPracticeName»
 «GPAddress1»
 «GPAddress2»
 «GPCity»
 «GPPostCode»

Dear «GPTitle» «GPSurname»

Re. «patName»
 «PatAddress1» «PatAddress2» «PatAddress3» «PatCity» «PatDistrict»
 «PatPostCode»

Thank you very much for letting us know about «PatTitle» «PatSurname»'s recent diagnosis of an intracranial vascular malformation (IVM). We will now start our process of carefully validating the diagnosis, and approaching the patient for his consent to participate in this observational study if you and their hospital consultant deem them suitable for postal consent.

Many Thanks,

Yours Sincerely,

Dr Rustam Al-Shahi
MRC Clinical Training Fellow
 SIVMS No.«PatID»

Prof. Charles P. Warlow
Professor of Medical Neurology

Department of Clinical Neurosciences
 Bramwell Dott Building
 Western General Hospital
 Crewe Road
 Edinburgh EH4 2XU
 tel/fax: 0131 537 2944
 e-mail: sivms@skull.dcn.ed.ac.uk
 web: <http://www.dcn.ed.ac.uk/ivm/>



19 February, 2003

«GPTitle» «GPForename» «GPSurname»
 «GPPracticeName»
 «GPAddress1»
 «GPAddress2»
 «PatAddress3»
 «GPCity»
 «GPPostCode»

Dear «GPTitle» «GPSurname»,

Re. «PatName»,
 «PatAddress1» «PatAddress2» «PatAddress3» «PatCity» «PatPostCode»

Your patient, «PatTitle» «PatSurname», was considered for inclusion in the Scottish Intracranial Vascular Malformation Study. Because you may have spoken or written to her about the study, we wanted to let you know that she has, in fact, been excluded because she does not have one of the diagnoses we are looking for. Feel free to contact us should you have any questions.

Yours Sincerely,

Dr Rustam Al-Shahi
MRC Clinical Training Fellow
 SIVMS No.«PatID»

Prof. Charles P. Warlow
Professor of Medical Neurology

Department of Clinical Neurosciences
 Bramwell Dott Building
 Western General Hospital
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 tel/fax: 0131 537 2944
 e-mail: sivms@skull.dcn.ed.ac.uk
 web: <http://www.dcn.ed.ac.uk/ivm/>



19 February, 2003

«CollTitle» «CollForename» «CollSurname»
 «CentreName»
 «CentreAddr1»
 «CentreAddr2»
 «CentreCity» «CentrePostCode»

Dear «CollTitle» «CollSurname»,

**Re. «PatTitle» «PatForename» «PatSurname»,
 «PatAddress1» «PatAddress2» «PatAddress3» «PatCity» «PatPostCode»**

Your patient, «PatTitle» «PatSurname», was considered for inclusion in the Scottish Intracranial Vascular Malformation Study. Because you may have spoken or written to her about the study, we wanted to let you know that she has, in fact, been excluded because she does not have one of the diagnoses we are looking for. Feel free to contact us should you have any questions.

Many Thanks,

Yours Sincerely,

Dr Rustam Al-Shahi
MRC Clinical Training Fellow
 SIVMS No.«PatID»

Prof. Charles P. Warlow
Professor of Medical Neurology

Department of Clinical Neurosciences
Bramwell Dott Building
Western General Hospital
Crewe Road
Edinburgh EH4 2XU
tel/fax: 0131 537 2944
e-mail: sivms@skull.dcn.ed.ac.uk
web: <http://www.dcn.ed.ac.uk/ivm/>



19 February, 2003

«CollTitle» «CollForename» «CollSurname»
«CentreName»
«CentreAddr1»
«CentreAddr2»
«CentreCity» «CentrePostCode»

Dear «CollTitle» «CollSurname»,

**Re. «PatTitle» «PatForename» «PatSurname», DOB «PatDOB»
«PatAddress1» «PatAddress2» «PatAddress3» «PatCity» «PatPostCode»**

Thank you very much for letting us know about «PatTitle» «PatSurname» for the purposes of our study. Since you may have spoken or written to «PatTitle» «PatSurname» about the study, we wanted to let you know that she has, in fact, been excluded because she does not have one of the diagnoses we are looking for, and we will not be approaching her to join the study.

Many Thanks,

Yours Sincerely,

Dr Rustam Al-Shahi
MRC Clinical Training Fellow
SIVMS No.«PatID»

Prof. Charles P. Warlow
Professor of Medical Neurology

Department of Clinical Neurosciences
 Bramwell Dott Building
 Western General Hospital
 Crewe Road
 Edinburgh EH4 2XU
 tel/fax: 0131 537 2944
 e-mail: sivms@skull.dcn.ed.ac.uk
 web: <http://www.dcn.ed.ac.uk/ivm/>



19 February, 2003

«GPTitle» «GPForename» «GPSurname»
 «GPPracticeName»
 «GPAddress1»
 «GPAddress2»
 «PatAddress3»
 «GPCity»
 «GPPostCode»

Dear «GPTitle» «GPSurname»,

**Re. «PatTitle» «PatForename» «PatSurname»
 «PatAddress1» «PatAddress2» «PatAddress3» «PatCity» «PatPostCode»**

Thank you very much for letting us know about «PatTitle» «PatSurname» for the purposes of our study. Since you may have spoken or written to «PatTitle» «PatSurname» about the study, we wanted to let you know that he has, in fact, been excluded because he does not have one of the diagnoses we are looking for, and we will not be approaching him to join the study.

Many Thanks,

Yours Sincerely,

Dr Rustam Al-Shahi
MRC Clinical Training Fellow
 SIVMS No.«PatID»

Prof. Charles P. Warlow
Professor of Medical Neurology

Department of Clinical Neurosciences
 Bramwell Dott Building
 Western General Hospital
 Crewe Road
 Edinburgh EH4 2XU
 tel/fax: 0131 537 2944
 e-mail: sivms@skull.dcn.ed.ac.uk
 web: <http://www.dcn.ed.ac.uk/ivm/>



19 February, 2003

«collName»
 «Department»
 «CentreName»
 «CentreAddr1»
 «CentreAddr2»
 «CentreCity» «CentrePostCode»

Dear «CollTitle» «CollSurname»

Re. «patientName»
 «PatAddress1» «PatAddress2» «PatAddress3», «PatCity» «PatPostCode»

«PatTitle» «PatSurname» under your care has been put forward for the Register of the Scottish Intracranial Vascular Malformation Study (SIVMS). We are writing to ask you to check the accuracy of the information we have been supplied with, and ensure that «PatTitle» «PatSurname» is still alive and aware of her diagnosis. Please could you also indicate whether it is appropriate to approach her by post and whether you are happy for us to have access to her hospital records for the purpose of this research project?

SIVMS is a prospective, observational study of **all** patients in Scotland diagnosed with **any type** of intracranial vascular malformation (IVM) after 1st January 1999. The study is based in the departments of Neuroradiology, Neurology, Neurosurgery and Neuropathology in all four Scottish Neuroscience centres. Our collaborative network also encompasses all the other Radiology Departments in the country. We aim to register **all** patients with an IVM in Scotland to better define the epidemiology of these rare, but important conditions. Data will be collected from individuals' medical records. Copies of their angiograms will be stored for further analysis. As of January 2001, of the patients we approach, 11% do not reply to our enrolment letter, only 2% decline to complete an annual questionnaire, and 87% agree to participate and complete annual questionnaires. We will be sending the patient's GP a *very brief* annual questionnaire to determine if the patient is still alive and, if so, whether they have been admitted to hospital in the preceding year. If they are still alive and appropriate for continued follow-up, the patient will receive an annual quality of life questionnaire if they have already agreed to receive it. There will be no additional therapeutic interventions over and above the care they are already receiving. **Patient confidentiality will be respected at all times. We have the approval of the Multicentre Research Ethics Committee for Scotland and your Local Research Ethics Committee.**

Would you please complete the enclosed five-step form and return it to us at your earliest convenience in the freepost envelope supplied. Do not hesitate to contact us if you have any further questions.

Yours Sincerely,

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

Prof Charles P Warlow
Professor of Medical Neurology

g:\trialdev\sivms\materials\enrollment\consultant reg letter.doc SIVMS No. «PatID»

Patient name	«patientName»
---------------------	---------------

Date of birth «PatDOB»

Patient address	«PatAddress1» «PatAddress2» «PatAddress3» «PatCity» «PatPostCode»
------------------------	---

IVM type	«IVMType»
----------	-----------

Date of *first* diagnosis 07/06/00

Please tick (✓) appropriate box

Yes	No
-----	----

«patientName» is still alive

9

9

She is aware of her diagnosis of an IVM (as above)

1

9

I agree to grant access to her GP records for the purpose of this research project

☐

It is appropriate to send her a postal consent form, if her consultant also approves

☐☐

If 'No', please comment:

Signature _____ Date _____
day/month/year

```
«gpName»
«GPPracticeName»
«GPAddress1»
«GPAddress2»
«GPCity»
«GPRegion»
«GPPostCode»
```

Please return this form in the freepost envelope provided to: SIVMS, Department of Clinical Neurosciences, Western General Hospital, Crewe Road, Edinburgh EH4 2XU

Department of Clinical Neurosciences
 Bramwell Dott Building
 Western General Hospital
 Crewe Road
 Edinburgh EH4 2XU
 tel/fax: 0131 537 2944
 e-mail: sivms@skull.dcn.ed.ac.uk
 web: <http://www.dcn.ed.ac.uk/ivm/>



19 February, 2003

«collName»
 «Department»
 «CentreName»
 «CentreAddr1»
 «CentreAddr2»
 «CentreCity» «CentrePostCode»

Dear «CollTitle» «CollSurname»

Re. «patientName»
 «PatAddress1» «PatAddress2» «PatAddress3», «PatCity» «PatPostCode»

Thank you very much for letting us know about «PatTitle» «PatSurname»'s recent diagnosis of an intracranial vascular malformation (IVM). We are writing to ask you to check the accuracy of the information we have, and ensure that «PatTitle» «PatSurname» is still alive and aware of her diagnosis. Please could you also indicate whether it is appropriate to approach her by post and whether you are happy for us to have access to her hospital records for the purpose of this research project?

SIVMS is a prospective, observational study of **all** patients in Scotland diagnosed with **any type** of intracranial vascular malformation (IVM) after 1st January 1999. The study is based in the departments of Neuroradiology, Neurology, Neurosurgery and Neuropathology in all four Scottish Neuroscience centres. Our collaborative network also encompasses all the other Radiology Departments in the country. We aim to register **all** patients with an IVM in Scotland to better define the epidemiology of these rare, but important conditions. Data will be collected from individuals' medical records. Copies of their angiograms will be stored for further analysis. As of January 2001, of the patients we approach, 11% do not reply to our enrolment letter, only 2% decline to complete an annual questionnaire, and 87% agree to participate and complete annual questionnaires. We will be sending the patient's GP a *very brief* annual questionnaire to determine if the patient is still alive and, if so, whether they have been admitted to hospital in the preceding year. If they are still alive and appropriate for continued follow-up, the patient will receive an annual quality of life questionnaire if they have already agreed to receive it. There will be no additional therapeutic interventions over and above the care they are already receiving. **Patient confidentiality will be respected at all times. We have the approval of the Multicentre Research Ethics Committee for Scotland and your Local Research Ethics Committee.**

Would you please complete the enclosed five-step form and return it to us at your earliest convenience in the freepost envelope supplied. Do not hesitate to contact us if you have any further questions.

Yours Sincerely,

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

Prof Charles P Warlow
Professor of Medical Neurology

g:\trialdev\sivms\materials\enrollment\consultant reg letter notif.doc SIVMS No. «PatID»

Patient name «patientName»
Date of birth «PatDOB»
Patient address «PatAddress1»
«PatAddress2»
«PatAddress3»
«PatCity»
«PatDistrict»
«PatPostCode»
IVM type «IVMType»
Date of *first* diagnosis «Notif1stDiagDate»

	Please tick (✓) appropriate box	
	Yes	No
) «PatTitle» «PatSurname» is still alive	<input type="checkbox"/>	<input type="checkbox"/>
) She is aware of her diagnosis of an IVM (as above)	<input type="checkbox"/>	<input type="checkbox"/>
) I agree to grant access to her hospital records for the purpose of this research project	<input type="checkbox"/>	<input type="checkbox"/>
) It is appropriate to send her a postal consent form, if her GP also approves	<input type="checkbox"/>	<input type="checkbox"/>

If 'No', please comment:
.....

) **Signature** _____ **Date** _____
day/month/year

«collName»
«Department»
«CentreName»
«CentreAddr1»
«CentreAddr2»
«CentreCity» «CentrePostCode»

Please return this form in the freepost envelope provided to: SIVMS, Department of Clinical Neurosciences, Western General Hospital, Crewe Road, Edinburgh EH4 2XU

Department of Clinical Neurosciences
 Bramwell Dott Building
 Western General Hospital
 Crewe Road
 Edinburgh EH4 2XU
 tel/fax: 0131 537 2944
 e-mail: sivms@skull.dcn.ed.ac.uk
 web: <http://www.dcn.ed.ac.uk/ivm/>



19 February, 2003

«collName»
 «Department»
 «CentreName»
 «CentreAddr1»
 «CentreAddr2»
 «CentreCity» «CentreRegion» «CentrePostCode»

Dear «CollTitle» «CollSurname»

Re. «patientName»
 «PatAddress1» «PatAddress2» «PatAddress3» «PatCity» «PatDistrict»
 «PatPostCode»

«PatTitle» «PatSurname», who has been under your care and died on «PatDeathDate», has been put forward for the Register of the Scottish Intracranial Vascular Malformation Study (SIVMS). We are writing to ask you to check the accuracy of the information we have been supplied with, and to ask for access to his hospital records for the purpose of this research project.

- SIVMS is a prospective, observational study of **all** patients in Scotland diagnosed with **any type** of intracranial vascular malformation (IVM) after 1st January 1999. The study is based in the departments of Neuroradiology, Neurology, Neurosurgery and Neuropathology in all four Scottish Neuroscience centres. Our collaborative network also encompasses all the other Radiology Departments in the country. We aim to register **all** patients with an IVM in Scotland to better define the epidemiology of these rare, but important conditions. Data will be collected from individuals' medical records. Copies of their imaging will be stored for further analysis. **Patient confidentiality will be respected at all times. We have the approval of the Multicentre Research Ethics Committee for Scotland and your Local Research Ethics Committee.**

Would you please complete the enclosed three-step form and return it to us at your earliest convenience in the freepost envelope supplied. Do not hesitate to contact us if you have any further questions.

Yours Sincerely,

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

Prof Charles P Warlow
Professor of Medical Neurology

g:\trialdev\sivms\materials\enrollment\consultant reg letter (dead)2.doc. SIVMS No.«PatID»

Patient name

«patientName»

Date of birth

«PatDOB»

Date of death

«PatDeathDate»

Patient address

«PatAddress1»
«PatAddress2»
«PatAddress3»
«PatCity»
«PatDistrict»
«PatPostCode»

IVM type

«IVMType»

Date of *first* diagnosis

Unknown

Please tick (✓)
appropriate box

Yes

No

) «PatTitle» «PatSurname» is dead

☐

☐

) I agree to grant access to her hospital records for the purpose of this research project

☐

☐

If 'No', please comment:

.....

)

Signature

Date

day/month/year

«collName»
«Department»
«CentreName»
«CentreAddr1»
«CentreAddr2»
«CentreCity» «CentreRegion» «CentrePostCode»

Please return this form in the freepost envelope provided to: SIVMS, Department of Clinical Neurosciences, Western General Hospital, Crewe Road, Edinburgh EH4 2XU

Department of Clinical Neurosciences
 Bramwell Dott Building
 Western General Hospital
 Crewe Road
 Edinburgh EH4 2XU
 tel/fax: 0131 537 2944
 e-mail: sivms@skull.dcn.ed.ac.uk
 web: <http://www.dcn.ed.ac.uk/ivm/>



19 February, 2003

«collName»
 «Department»
 «CentreName»
 «CentreAddr1»
 «CentreAddr2»
 «CentreCity» «CentreRegion» «CentrePostCode»

Dear «CollTitle» «CollSurname»

Re. «patientName»
 «PatAddress1» «PatAddress2» «PatAddress3» «PatCity» «PatDistrict»
 «PatPostCode»

Thank you very much for letting us know about «PatTitle» «PatSurname»'s recent diagnosis of an intracranial vascular malformation (IVM) for the purposes of the Scottish Intracranial Vascular Malformation Study (SIVMS). Because they were under your care and died on «PatDeathDate», we are writing to ask you to check the accuracy of the information we have been supplied with, and to ask for access to «PatTitle» «PatSurname»'s hospital records for the purpose of this research project.

SIVMS is a prospective, observational study of **all** patients in Scotland diagnosed with **any type** of intracranial vascular malformation (IVM) after 1st January 1999. The study is based in the departments of Neuroradiology, Neurology, Neurosurgery and Neuropathology in all four Scottish Neuroscience centres. Our collaborative network also encompasses all the other Radiology Departments in the country. We aim to register **all** patients with an IVM in Scotland to better define the epidemiology of these rare, but important conditions. Data will be collected from individuals' medical records. Copies of their imaging will be stored for further analysis. **Patient confidentiality will be respected at all times.** **We have the approval of the Multicentre Research Ethics Committee for Scotland and your Local Research Ethics Committee.**

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Yours Sincerely,

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

Prof Charles P Warlow
Professor of Medical Neurology

g:\trialdev\sivms\materials\enrollment\consultant reg letter (dead)2 notif.doc. SIVMS No. «PatID»

Patient name «patientName»
Date of birth «PatDOB»
Date of death «PatDeathDate»
Patient address «PatAddress1»
«PatAddress2»
«PatAddress3»
«PatCity»
«PatDistrict»
«PatPostCode»
IVM type «IVMType»
Date of *first* diagnosis Unknown

Please tick (✓)
appropriate box
Yes No

-) «PatTitle» «PatSurname» is dead ☐ ☐
-) I agree to grant access to her hospital records for the purpose of this research project ☐ ☐

If 'No', please comment:

.....

) **Signature** _____ **Date** _____
day/month/year

«collName»
«Department»
«CentreName»
«CentreAddr1»
«CentreAddr2»
«CentreCity» «CentreRegion» «CentrePostCode»

Please return this form in the freepost envelope provided to: SIVMS, Department of Clinical Neurosciences, Western General Hospital, Crewe Road, Edinburgh EH4 2XU

Department of Clinical Neurosciences
 Bramwell Dott Building
 Western General Hospital
 Crewe Road
 Edinburgh EH4 2XU
 tel/fax: 0131 537 2944
 e-mail: sivms@skull.dcn.ed.ac.uk
 web: <http://www.dcn.ed.ac.uk/ivm/>



19 February 2003

«collName»
 «Department»
 «CentreName»
 «CentreAddr1»
 «CentreAddr2»
 «CentreCity» «CentrePostCode»

Dear «CollTitle» «CollSurname»

Re. «patientName»
 «PatAddress1» «PatAddress2» «PatAddress3» «PatCity» «PatPostCode»

«PatTitle» «PatSurname», who has been under your care, has been put forward for the Register of the Scottish Intracranial Vascular Malformation Study (SIVMS). We are writing to ask you to check the accuracy of the information we have been supplied with, and ensure that «PatTitle» «PatSurname» is still alive and aware of his diagnosis. Please could you also indicate whether it is appropriate to approach him by post and whether you are happy for us to have access to his hospital records for the purpose of this research project?

SIVMS is a prospective, observational study of **all** patients in Scotland diagnosed with **any type** of intracranial vascular malformation (IVM) after 1st January 1999. The study is based in the departments of Neuroradiology, Neurology, Neurosurgery and Neuropathology in all four Scottish Neuroscience centres. Our collaborative network also encompasses all the other Radiology Departments in the country. We aim to register **all** patients with an IVM in Scotland to better define the epidemiology of these rare, but important conditions. Data will be collected from individuals' medical records. Copies of their angiograms will be stored for further analysis. As of January 2001, of the patients we approach, 11% do not reply to our enrolment letter, only 2% decline to complete an annual questionnaire, and 87% agree to participate and complete annual questionnaires. We will be sending the patient's GP a *very brief* annual questionnaire to determine if the patient is still alive and, if so, whether they have been admitted to hospital in the preceding year. If they are still alive and appropriate for continued follow-up, the patient will receive an annual quality of life questionnaire if they have already agreed to receive it. There will be no additional therapeutic interventions over and above the care they are already receiving. **Patient confidentiality will be respected at all times. We have the approval of the Multicentre Research Ethics Committee for Scotland and your Local Research Ethics Committee.**

If you have referred «PatTitle» «PatSurname» to a Neurologist or Neurosurgeon, please let us know who they are so that we can seek their consent for this patient's enrolment in our study. If not, would you please complete the enclosed five-step form and return it to us at your earliest convenience in the freepost envelope supplied.

Yours Sincerely,

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

Prof Charles P Warlow
Professor of Medical Neurology

g:\trialdev\sivms\materials\enrollment\consultant reg letter not neuro (alive).doc SIVMS No. «PatID»

Patient name «patientName»

Date of birth «PatDOB»

Patient address «PatAddress1»
«PatAddress2»
«PatAddress3»
«PatCity»
«PatDistrict»
«PatPostCode»

IVM type «IVMType»

Date of *first* diagnosis «Notif1stDiagDate»

	Please tick (✓) appropriate box	
	Yes	No
) «PatTitle» «PatSurname» is still alive	<input type="checkbox"/>	<input type="checkbox"/>
) She is aware of her diagnosis of an IVM (as above)	<input type="checkbox"/>	<input type="checkbox"/>
) I agree to grant access to her hospital records for the purpose of this research project	<input type="checkbox"/>	<input type="checkbox"/>
) It is appropriate to send her a postal consent form, if her GP also approves	<input type="checkbox"/>	<input type="checkbox"/>

If 'No', please comment:

.....

) **Signature** _____ **Date** _____
day/month/year

«collName»
«Department»
«CentreName»
«CentreAddr1»
«CentreAddr2»
«CentreCity» «CentrePostCode»

Please return this form in the freepost envelope provided to: SIVMS, Department of Clinical Neurosciences, Western General Hospital, Crewe Road, Edinburgh EH4 2XU

Department of Clinical Neurosciences
 Bramwell Dott Building
 Western General Hospital
 Crewe Road
 Edinburgh EH4 2XU
 tel/fax: 0131 537 2944
 e-mail: sivms@skull.dcn.ed.ac.uk
 web: <http://www.dcn.ed.ac.uk/ivm/>



19 February 2003

«collName»
 «Department»
 «CentreName»
 «CentreAddr1»
 «CentreAddr2»
 «CentreCity»
 «CentreRegion» «CentrePostCode»

Dear «CollTitle» «CollSurname»

Re. «patientName»
 «PatAddress1» «PatAddress2» «PatAddress3» «PatCity» «PatDistrict»
 «PatPostCode»

«PatTitle» «PatSurname», who has been under your care and died on «PatDeathDate», has been put forward for the Register of the Scottish Intracranial Vascular Malformation Study (SIVMS). We are writing to ask you to check the accuracy of the information we have been supplied with, and to ask for access to «PatTitle» «PatSurname»'s hospital records for the purpose of this research project.

SIVMS is a prospective, observational study of **all** patients in Scotland diagnosed with **any type** of intracranial vascular malformation (IVM) after 1st January 1999. The study is based in the departments of Neuroradiology, Neurology, Neurosurgery and Neuropathology in all four Scottish Neuroscience centres. Our collaborative network also encompasses all the other Radiology Departments in the country. We aim to register **all** patients with an IVM in Scotland to better define the epidemiology of these rare, but important conditions. Data will be collected from individuals' medical records. Copies of their imaging will be stored for further analysis. **Patient confidentiality will be respected at all times. We have the approval of the Multicentre Research Ethics Committee for Scotland and your Local Research Ethics Committee.**

If a Neurologist or Neurosurgeon looked after «PatTitle» «PatSurname» prior to his death, please let us know who they are so that we can seek their consent for this patient's enrolment in our study. If not, would you please complete the enclosed three-step form and return it to us at your earliest convenience in the freepost envelope supplied. Do not hesitate to contact us if you have any further questions.

Yours Sincerely,

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

Prof Charles P Warlow
Professor of Medical Neurology

g:\trialdev\sivms\materials\enrollment\consultant reg letter not neuro (dead).doc. SIVMS No. «PatID»

Patient name

«patientName»

Date of birth

«PatDOB»

Date of death

«PatDeathDate»

Patient address

«PatAddress1»

«PatAddress2»

«PatAddress3»

«PatCity»

«PatDistrict»

«PatPostCode»

IVM type

«IVMType»

Date of *first* diagnosis

«Notif1stDiagDate»

Please tick (✓)
appropriate box

Yes

No

)

«PatTitle» «PatSurname» is dead

☐

☐

)

I agree to grant access to his hospital records for the purpose of this research project

☐

☐

If 'No', please comment:

.....

)

Signature

Date

day/month/year

«collName»

«Department»

«CentreName»

«CentreAddr1»

«CentreAddr2»

«CentreCity» «CentreRegion»

«CentrePostCode»

Please return this form in the freepost envelope provided to: SIVMS, Department of Clinical Neurosciences, Western General Hospital, Crewe Road, Edinburgh EH4 2XU

Department of Clinical Neurosciences
 Bramwell Dott Building
 Western General Hospital
 Crewe Road
 Edinburgh EH4 2XU
 tel/fax: 0131 537 2944
 e-mail: sivms@skull.dcn.ed.ac.uk
 web: <http://www.dcn.ed.ac.uk/ivm/>



19 February, 2003

«RegCollName»
 «Department»
 «RegCentreName»
 «CentreAddr1»
 «CentreAddr2»
 «CentreCity» «CentrePostCode»

Dear «CollTitle» «CollSurname»

Re. «patientName»
 «PatAddress1» «PatAddress2» «PatAddress3», «PatCity» «PatPostCode»

«PatTitle» «PatSurname», who has been under your care, has been put forward for the Register of the Scottish Intracranial Vascular Malformation (IVM) Study. Although «PatTitle» «PatSurname» is also under the care of «mainCons» at the «MainCentre» for his IVM(s), we are writing to ask for access to his medical records at your hospital for the purpose of this research project.

SIVMS is a prospective, observational study of **all** patients in Scotland diagnosed with **any type** of intracranial vascular malformation (IVM) after 1st January 1999. The study is based in the departments of Neuroradiology, Neurology, Neurosurgery and Neuropathology in all four Scottish Neuroscience centres. Our collaborative network also encompasses all the other Radiology Departments in the country. We aim to register **all** patients with an IVM in Scotland to better define the epidemiology of these rare, but important conditions. Data will be collected from individuals' medical records. Copies of their angiograms will be stored for further analysis. As of January 2001, of the patients we approach, 11% do not reply to our enrolment letter, only 2% decline to complete an annual questionnaire, and 87% agree to participate and complete annual questionnaires. We will be sending the patient's GP a *very brief* annual questionnaire to determine if the patient is still alive and, if so, whether they have been admitted to hospital in the preceding year. If they are still alive and appropriate for continued follow-up, the patient will receive an annual quality of life questionnaire if they have already agreed to receive it. There will be no additional therapeutic interventions over and above the care they are already receiving. **Patient confidentiality will be respected at all times. We have the approval of the Multicentre Research Ethics Committee for Scotland and your Local Research Ethics Committee.**

Could you please complete the enclosed two-step form and return it to us at your earliest convenience in the freepost envelope supplied. Do not hesitate to contact us if you have any further questions.

Yours Sincerely,

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

Prof Charles P Warlow
Professor of Medical Neurology

g:\trialdev\sivms\materials\enrollment\consultant reg letter (another centre)2.doc SIVMS No.«PatID»

Patient name	«patientName»
---------------------	---------------

Date of birth «PatDOB»

Patient address	«PatAddress1»
	«PatAddress2»
	«PatAddress3»
	«PatCity»
	«PatDistrict»
	«PatPostCode»

IVM type	«IVMType»
----------	-----------

Date of *first* diagnosis Unknown

**Please tick (✓)
appropriate box**

Yes

No

I agree to grant access «PatTitle» «PatSurname»'s hospital records for the purpose of this research project

If 'No', please comment:

Signature _____ Date _____
day/month/year

«RegCollName»
«Department»
«RegCentreName»
«CentreAddr1»
«CentreAddr2»
«CentreCity» «CentrePostCode»

Please return this form in the freepost envelope provided to: SIVMS, Department of Clinical Neurosciences, Western General Hospital, Crewe Road, Edinburgh EH4 2XU

Department of Clinical Neurosciences
Bramwell Dott Building
Western General Hospital
Crewe Road
Edinburgh EH4 2XU
tel/fax: 0131 537 2944
e-mail: sivms@skull.dcn.ed.ac.uk
web: <http://www.dcn.ed.ac.uk/ivm/>



19 February, 2003

«TITLE» «INITS» «tblISDConsultantsNAME»
Department of Neurosurgery
«tblISDHospitalsNAME»
«A_1»
«A_2»
«A_3» «POSTCODE»

Dear «TITLE» «tblISDConsultantsNAME»,

Re. Ms «Field10» «Field9»
Date of birth «DateOfBirth»
Postcode «Field14»
Case reference number «Field7»
Date of admission «DateAdmission»
Date of discharge «DateDischarge»

We would be very grateful for your help with the Scottish Intracranial Vascular Malformation Study (SIVMS) to establish the incidence of *all* people affected by *any type* of intracranial vascular malformation (IVM) in the Scottish population. We have the full approval of the relevant ethics committees. We may have been in touch with you before, in which case we are sorry if any information has been duplicated.

We believe that «Field10» «Field9» was diagnosed with a/an «IVM» whilst under your care between «DateAdmission» and «DateDischarge». We are writing to ask if you would kindly check the accuracy of the information we have been supplied with. We have acquired this information from routine coding of hospital discharge data, which can occasionally be inaccurate. We would be very grateful if you could complete the enclosed form and return it to us at your earliest convenience in the freepost envelope supplied. If the diagnostic information is inaccurate, we are sorry to have bothered you unnecessarily, but please return the form anyway. Do not hesitate to contact us if you have any questions. Thank you in advance for your help.

Inclusion criteria
1 st diagnosed AFTER 1 JANUARY 99
Any type of IVM, affecting the brain:
Arteriovenous malformation (AVM)
Cavernous malformation/cavernoma (CM)
Venous malformation/anomaly (VM)
Dural arteriovenous fistula (DAVF)
Resident in Scotland
Age 16 years or over at diagnosis
Exclusion criteria
An aneurysm ON ITS OWN

Yours Sincerely,

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

Prof. Charles P. Warlow
Professor of Medical Neurology

\\dcn-skull\\vol1\\trialdev\\sivms\\i.s.d\\consultant isd inquiry.doc Link number «Field1»

Patient Name«Field10» «Field9»

Date of Birth«DateOfBirth»

		Please tick (✓) appropriate box	
		Yes	No
Resident in Scotland at	«Field14»	<input type="checkbox"/>	<input type="checkbox"/>
IVM type	«IVM»	<input type="checkbox"/>	<input type="checkbox"/>
Date of FIRST EVER diagnosis	between «Admission» and «Discharge»	<input type="checkbox"/>	<input type="checkbox"/>
«Field10» «Field9» is still alive		<input type="checkbox"/>	<input type="checkbox"/>

If any of the answers to questions 1-4 were 'No', please comment here...

.....

She is aware of her diagnosis of an IVM (as above)	<input type="checkbox"/>	<input type="checkbox"/>
I am willing to grant access to her hospital records just for the purpose of this research project	<input type="checkbox"/>	<input type="checkbox"/>
Is it appropriate to approach her with a postal consent form and information leaflet, if her GP also approves?	<input type="checkbox"/>	<input type="checkbox"/>

If 'No', please comment:

.....

If you are no longer looking after «Field10» «Field9», please let us know which consultant is looking after her:

.....

Signature_____Date_____

day/month/year
Sent: 19/02/03

«TITLE» «INITS» «tblISDConsultantsNAME»
Department of ???
«tblISDHospitalsNAME»
«A_1»
«A_2»
«A_3» «POSTCODE»

Please return this form in the freepost envelope provided to: SIVMS, Department of Clinical Neurosciences, Western General Hospital, Crewe Road, Edinburgh EH4 2XU

Department of Clinical Neurosciences
 Bramwell Dott Building
 Western General Hospital
 Crewe Road
 Edinburgh EH4 2XU
 tel/fax: 0131 537 2944
 e-mail: sivms@skull.dcn.ed.ac.uk
 web: <http://www.dcn.ed.ac.uk/ivm/>



13 March, 2003

«gpName»
 «GPPPracticeName»
 «GPAddress1»
 «GPAddress2»
 «GPCity» «GPPostCode»

Dear «GPTitle» «GPSurname»

Re. «patientName»
 «PatAddress1» «PatAddress2» «PatAddress3» «PatCity» «PatPostCode»

We would like to contact «PatTitle» «PatSurname», who has been put forward for the Register of the Scottish Intracranial Vascular Malformation Study (SIVMS). We are often told about new cases by Radiologists, so you may receive this letter before seeing the imaging report or hospital correspondence. We are writing to ask if you would kindly check the accuracy of the information we have been supplied with and that «PatTitle» «PatSurname» is still alive and aware of her diagnosis. Please could you also indicate whether it is appropriate to approach her by post and whether you are happy for us to have access to her GP records for the purpose of this research project only (we are happy to discuss remuneration)?

SIVMS is a prospective, observational study of **all** patients in Scotland with **any type** of intracranial vascular malformation (IVM). The study is based in all four Scottish Neuroscience centres and our collaborative network also encompasses all the other Radiology Departments in the country. We aim to register **all** patients with an IVM in Scotland to better define the epidemiology of these rare, but important conditions. Data will be collected from individuals' medical records. As of January 2001, of the patients we approach, 11% do not reply to our enrolment letter, only 2% decline to complete an annual questionnaire, and 87% agree to participate and complete annual questionnaires. We would like to send you a *very brief* annual questionnaire to collect vital follow-up information about «patientName» that may only be known to you. If the patient is still alive and appropriate for continued follow-up, they will receive an annual quality of life questionnaire if they have already agreed to receive it. There will be no additional therapeutic interventions over and above the care they are already receiving. For your interest, the protocol is enclosed.

Patient confidentiality will be respected at all times. We have the approval of the Multicentre Research Ethics Committee for Scotland and your Local Research Ethics Committee.

We would be very grateful if you could complete the enclosed five-step form and return it to us in the freepost envelope supplied. Do contact us if you have any further questions.

Yours Sincerely,

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

Prof Charles P Warlow
Professor of Medical Neurology

g:\trialdev\sivms\materials\enrollment\gp reg letter2.doc SIVMS No.«PatID»

Patient name	«patientName»
---------------------	---------------

Date of birth «PatDOB»

Patient address	«PatAddress1»
	«PatAddress2»
	«PatAddress3»
	«PatCity»
	«PatPostCode»

IVM type	«IVMType»
----------	-----------

Date of *first* diagnosis 07/06/00

Please tick (✓) appropriate box

Yes	No
-----	----

«patientName» is still alive

10/10

She is aware of her diagnosis of an IVM (as above)

□ □

I agree to grant access to her GP records for the purpose of this research project

11

It is appropriate to send her a postal consent form, if her consultant also approves

10/10

If **'No'**, please comment:

Signature _____ **Date** _____
day/month/year

```
«gpName»
«GPPracticeName»
«GPAddress1»
«GPAddress2»
«GPCity»
«GPRegion»
«GPPostCode»
```

Please return this form in the freepost envelope provided to: SIVMS, Department of Clinical Neurosciences, Western General Hospital, Crewe Road, Edinburgh EH4 2XU

Department of Clinical Neurosciences
 Bramwell Dott Building
 Western General Hospital
 Crewe Road
 Edinburgh EH4 2XU
 tel/fax: 0131 537 2944
 e-mail: sivms@skull.dcn.ed.ac.uk
 web: <http://www.dcn.ed.ac.uk/ivm/>



13 March, 2003

«gpName»
 «GPPPracticeName»
 «GPAddress1»
 «GPAddress2»
 «GPCity» «GPPostCode»

Dear «GPTitle» «GPSurname»

**Re. «patientName». DoB «PatDOB»
 «PatAddress1» «PatAddress2» «PatAddress3» «PatCity» «PatPostCode»**

We are about to contact «PatTitle» «PatSurname», whom you kindly put forward for the Register of the Scottish Intracranial Vascular Malformation Study (SIVMS). We are writing to ask you to check the accuracy of the information we have, and ensure that «PatTitle» «PatSurname» is still alive and aware of her diagnosis. Please could you also indicate whether it is appropriate to approach her by post and whether you are happy for us to have access to her GP records for the purpose of this research project only?

SIVMS is a prospective, observational study of **all** patients in Scotland diagnosed with **any type** of intracranial vascular malformation (IVM) after 1st January 1999. The study is based in the departments of Neuroradiology, Neurology, Neurosurgery and Neuropathology in all four Scottish Neuroscience centres. Our collaborative network also encompasses all the other Radiology Departments in the country. We aim to register **all** patients with an IVM in Scotland to better define the epidemiology of these rare, but important conditions. Data will be collected from individuals' medical records. Copies of their angiograms will be stored for further analysis. As of January 2001, of the patients we approach, 11% do not reply to our enrolment letter, only 2% decline to complete an annual questionnaire, and 87% agree to participate and complete annual questionnaires. We will be sending the patient's GP a very *brief* annual questionnaire to determine if the patient is still alive and, if so, whether they have been admitted to hospital in the preceding year. If they are still alive and appropriate for continued follow-up, the patient will receive an annual quality of life questionnaire if they have already agreed to receive it. There will be no additional therapeutic interventions over and above the care they are already receiving. **Patient confidentiality will be respected at all times. We have the approval of the Multicentre Research Ethics Committee for Scotland and your Local Research Ethics Committee.**

Would you please complete the enclosed five-step form and return it to us at your earliest convenience in the freepost envelope supplied. We enclose a copy of the study protocol. Do not hesitate to contact us at the number above if you have any further questions.

Yours Sincerely,

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

g:\trialdev\sivms\materials\enrolment\gp reg letter notifier.doc SIVMS No.«PatID»

Prof Charles P Warlow
Professor of Medical Neurology

Patient name	«patientName»
---------------------	---------------

Date of birth «PatDOB»

Patient address	«PatAddress1»
	«PatAddress2»
	«PatAddress3»
	«PatCity»
	«PatPostCode»

IVM type	«IVMType»
----------	-----------

Date of <i>first</i> diagnosis	Unknown
--------------------------------	---------

Please tick (✓)
appropriate box

Yes

No

«patientName» is still alive

☐☐

She is aware of her diagnosis of an IVM (as above)

☐☐

I agree to grant access to her GP records for the purpose of this research project

1

1

It is appropriate to send her a postal consent form, if her consultant also approves

7

☐

If 'No', please comment:

Signature _____ **Date** _____
day/month/year

day/month/year

```
«gpName»
«GPPracticeName»
«GPAddress1»
«GPAddress2»
«GPCity»
«GPRegion»
«GPPostCode»
```

Please return this form in the freepost envelope provided to: SIVMS, Department of Clinical Neurosciences, Western General Hospital, Crewe Road, Edinburgh EH4 2XU

Department of Clinical Neurosciences
 Bramwell Dott Building
 Western General Hospital
 Crewe Road
 Edinburgh EH4 2XU
 tel/fax: 0131 537 2944
 e-mail: sivms@skull.dcn.ed.ac.uk
 web: <http://www.dcn.ed.ac.uk/ivm/>



13 March, 2003

«gpName»
 «GPPPracticeName»
 «GPAddress1»
 «GPAddress2»
 «GPCity» «GPPostCode»

Dear «GPTitle» «GPSurname»

Re. «patientName»
 «PatAddress1» «PatAddress2» «PatAddress3», «PatCity» «PatPostCode»

«PatTitle» «PatSurname» has been put forward for the Register of the Scottish Intracranial Vascular Malformation Study (SIVMS). We are occasionally told about new cases by Pathologists, so you may receive this letter before seeing the post mortem report or hospital correspondence. We are writing to ask if you would kindly check the accuracy of the information we have been supplied with and, in particular, to ask for access to her GP medical records for the purpose of this research project only.

SIVMS is a prospective, observational study of **all** patients in Scotland with **any type** of intracranial vascular malformation (IVM). The study is based in all four Scottish Neuroscience centres and our collaborative network also encompasses all the other Radiology Departments in the country. We aim to register **all** patients with an IVM in Scotland to better define the epidemiology of these rare, but important conditions. Data will be collected from individuals' medical records. For your interest, we enclose a copy of the study protocol.

Patient confidentiality will be respected at all times. We have the approval of the Multicentre Research Ethics Committee for Scotland and your Local Research Ethics Committee.

We would be very grateful if you could complete the enclosed four-step form and return it to us in the freepost envelope supplied. Do contact us if you have any further questions.

Yours Sincerely,

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

Prof Charles P Warlow
Professor of Medical Neurology

\\dcn-skull\vol1\trialdev\sivms\materials\enrollment\gp reg letter (dead)2.doc SIVMS No. «PatID»

Patient name	«patientName»
Date of birth	«PatDOB»
Date of death	«PatDeathDate»
Patient address	«PatAddress1» «PatAddress2» «PatAddress3» «PatCity» «PatPostCode»

IVM type	«IVMType»
----------	-----------

Date of *first* diagnosis 05/11/99

Please tick (✓) appropriate box

	Yes	No
--	-----	----

«PatTitle» «PatSurname» is dead ☐ ☐

I agree to grant access to her GP records for the purpose of this research project only ☐ ☐

If 'No', please comment:

1) Please tell us where the GP notes are located (e.g. Practitioner Services or other)

Signature _____ **Date** _____
day/month/year

```
«gpName»
«GPPracticeName»
«GPAddress1»
«GPAddress2»
«GPCity»
«GPPostCode»
```

Please return this form in the freepost envelope provided to: SIVMS, Department of Clinical Neurosciences, Western General Hospital, Crewe Road, Edinburgh EH4 2XU

Department of Clinical Neurosciences
 Bramwell Dott Building
 Western General Hospital
 Crewe Road
 Edinburgh EH4 2XU
 tel/fax: 0131 537 2944
 e-mail: sivms@skull.dcn.ed.ac.uk
 web: <http://www.dcn.ed.ac.uk/ivm/>



13 March, 2003

«gpName»
 «GPPracticeName»
 «GPAddress1»
 «GPAddress2»
 «GPCity» «GPPostCode»

Dear «GPTitle» «GPSurname»,

Re. «patientName» Date of birth «PatDOB»
 «PatAddress1» «PatAddress2» «PatAddress3» «PatCity» «PatPostCode»

We believe «patientName» has recently become your patient. He is already registered with the Scottish Intracranial Vascular Malformation Study (SIVMS), because we have been told that he had a diagnosis of «IVMType» on 12/10/99. We would like to inform you about his inclusion in our study, and ask you to kindly return the attached sheet to us in the freepost envelope provided.

SIVMS is a prospective, observational study of **all** patients in Scotland with **any type** of intracranial vascular malformation (IVM). The study is based in all four Scottish Neuroscience centres and our collaborative network also encompasses all the other Radiology Departments in the country. We aim to register **all** patients with an IVM in Scotland to better define the prognosis and treatment of these rare, but important conditions. Data will be collected from individuals' medical records.

We would like to send you a *very brief* annual questionnaire to determine if «patientName» is still alive and if so, whether he has been admitted to hospital in the preceding year. If he is still alive and appropriate for continued follow-up, he will receive an annual quality of life questionnaire. There will be no additional therapeutic interventions over and above the care he is already receiving. For your interest, the protocol is enclosed.

Patient confidentiality will be respected at all times. We have the approval of the Multicentre Research Ethics Committee for Scotland and your Local Research Ethics Committee.

We would be very grateful to you for completing the enclosed form and returning it to us in the freepost envelope supplied. Do contact us if you have any further questions.

Yours Sincerely

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

g:\trialdev\sivms\materials\followup\gp has changed.doc SIVMS No.«PatID»

Prof Charles P Warlow
Professor of Medical Neurology

«patientName»'s last GP, «oldGP» at «oldPrac», «oldAdd1» «oldAdd2», «oldCity» gave us the following answers on «PatGPLetterResponse» - please amend or complete the answers if applicable:

Can we have access to «patientName»'s GP notes?	Yes
Did «oldGP» think «patientName» is aware of his diagnosis?	Yes
Overall decision (taking into account «CollTitle» «CollForename» «CollSurname»'s opinion) about whether «patientName» is aware of his diagnosis	Yes
Did «oldGP» think it appropriate to send «patientName» a consent form (and annual quality of life questionnaire, if he agrees)?	Yes
Overall decision (taking into account «CollTitle» «CollForename» «CollSurname»'s opinion) to approach «patientName» by post	No
Has «patientName» consented to join the study yet?	Yes

Please sign below and return this form to us in the freepost envelope provided, to indicate you agree with the above.

Signature _____ **Date** _____
day/month/year

«gpName»
 «GPPPracticeName»
 «GPAddress1»
 «GPAddress2»
 «GPCity»
 «GPRegion»
 «GPPostCode»

Please return this form in the freepost envelope provided to: SIVMS, Department of Clinical Neurosciences, Western General Hospital, Crewe Road, Edinburgh EH4 2XU

Department of Clinical Neurosciences
 Bramwell Dott Building
 Western General Hospital
 Crewe Road
 Edinburgh EH4 2XU
 tel/fax: 0131 537 2944
 e-mail: sivms@skull.dcn.ed.ac.uk
 web: <http://www.dcn.ed.ac.uk/ivm/>



13 March 2003

«GPTitle» «GPForename» «GPSurname»
 «GPPPracticeName»
 «GPAddress1»
 «GPAddress2»
 «GPCity» «GPPostCode»

Dear «GPTitle» «GPSurname»

Re. «name», «PatAddress1», «PatAddress2», «PatAddress3»
 «PatCity» «PatPostCode» Date of birth «PatDOB»

Thank you for replying to our last letter about «PatTitle» «PatSurname» on «PatGPLetterResponse».

We are sorry to have to bother you about our study again, but we would be grateful for your help to avoid "cold-calling" «PatTitle» «PatSurname» ourselves, yet obtain her consent to join our study to gain important information about the prognosis and treatment of her condition.

All we are asking you to do is to sign the enclosed letter from yourself to «PatTitle» «PatSurname», unless you wish to re-draft it, and post it with the enclosed package to her in the pre-paid envelope provided. The forms and pre-paid envelope are designed to make the task as easy and inexpensive for you as possible.

We are sorry to bother you with what we hope will be a small task. We have been instructed to approach patients in this way by the Multicentre Research Ethics Committee for Scotland. Do contact us if you have any questions or comments.

Thank you in advance for your support.

Yours Sincerely

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

Prof. Charles P. Warlow
Professor of Medical Neurology

g:\trialdev\sivms\materials\enrolment\patient recruitment letter.doc SIVMS No.«PatID»

«GPTitle» «GPForename» «GPSurname»
«GPPracticeName»
«GPAddress1»
«GPAddress2»
«GPCity» «GPPostCode»

13 March 2003

«name»
«PatAddress1»
«PatAddress2»
«PatAddress3»
«PatCity»
«PatPostCode»

Dear «PatTitle» «PatSurname»

I am writing to you on behalf of Professor Charles Warlow and colleagues in the Department of Clinical Neurosciences at the Western General Hospital in Edinburgh. They are running the Scottish Intracranial Vascular Malformation Study (SIVMS). SIVMS is a medical research study that gathers information about people with any type of intracranial vascular malformation, known as 'IVMs' for short. As a result of your recent tests at the «CentreName», they understand you may be affected by this medical condition.

Please could you read the enclosed information leaflet, which gives further information about the study? If you are willing to take part, I would be very grateful if you would complete the consent form and SIVMS Questionnaire, and return them in the enclosed freepost envelope to the study team in Edinburgh as soon as you can. They would be very pleased if you took part so that we can all find out more about IVMs and how to manage them better.

Thank you in advance for your support of their study.

Yours Sincerely

«GPTitle» «GPForename» «GPSurname»
«GPPracticeName»

Who organises and funds the research?

This study is sponsored by the UK Medical Research Council and the Chief Scientist Office of the Scottish Executive. The research team is based in Edinburgh, but the study is overseen by a Steering Committee with representatives from all over Scotland.

How can I obtain more information?

In this leaflet we have attempted to give you information on the scientific and ethical background of the study. Please contact the SIVMS team if you have any concerns about registration, if you want further information about IVMs, or if you decide to withdraw from the study.

For further information...

If you would like more information about any type of IVM, please contact us by telephone, fax, post or e-mail (details overleaf).

You may also seek advice about SIVMS from your hospital consultant or an independent adviser (see below).

Independent adviser

Professor Peter Sandercock is available for independent advice about this study at the address overleaf, or by telephoning 0131 537 2928.

Steering Committee

Aberdeen
Mr DG Currie

Dundee
Dr RC Roberts

Edinburgh
Dr R Al-Shahi, Dr V Ritchie,
Dr RJ Sellar, Professor CP Watlow

Glasgow
Dr JJ Bhattacharya, Mr V Papanastassiou



A register for people affected by vascular malformations of the brain in Scotland



Information leaflet

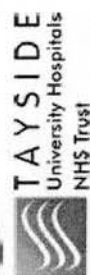
Version 2, May 2001



Bramwell Dott Building
Department of Clinical Neurosciences
Western General Hospital
Crewe Road
Edinburgh EH4 2XU



tel/fax: 0131 537 2944
e-mail: SIVMS@skull.dcn.ed.ac.uk
web: <http://www.dcn.ed.ac.uk/ivm/>



You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. We hope you will join our study.

Why have I been chosen?

One of the doctors involved in your care has told us that you have a type of 'intracranial vascular malformation', or 'IVM'. An IVM is a tangle of blood vessels in your brain. The different types of IVM are:

- ◆ Arteriovenous malformation (AVM)
- ◆ Cavernous malformation ('cavernoma' or 'cavernous angioma')
- ◆ Venous malformation ('venous anomaly')
- ◆ Dural arteriovenous fistula

So that we can find out more about these rare, but important conditions, we invite you to participate in 'SIVMS', the Scottish Intracranial Vascular Malformation Study.

What is the purpose of the study?

The aim of SIVMS is to find every person with an IVM in Scotland and enroll them in a confidential register. We only ask for a few minutes of your time each year.

Why do we need a register?

We are using the register to:

1. Find out how common IVMs are in Scotland
2. Find out what is important to you about having an IVM
3. Understand better the particular problems caused by IVMs over time

A large print version of this leaflet can be supplied

What will happen if I take part?

After you register, we will extract some basic information about your medical history from your medical records. If you agree, we will also send you a short questionnaire asking some simple questions about your day-to-day life. This should take only 20 minutes to complete. We may occasionally need to telephone you.

We need to find out what happens to people with your condition over long periods of time, and not just in the short term. Therefore we will need to look at your medical records from time to time. We would also like to send you a questionnaire every year, if appropriate, for the rest of your life.

If English is not your first language, this leaflet could be translated for you

Will the information be confidential?

Any information collected about you will be kept strictly confidential and used only for this study. These details will only be available to research staff, and no-one else. The published results of the research will not identify individual people. We comply with the Data Protection Act 1998. We have full ethical approval for this study from the Multi-centre Research Ethics Committee for Scotland and your Local Research Ethics Committee.

We assure you complete confidentiality

Do I have to take part?

It is up to you to decide whether or not to take part. Please complete and sign the enclosed registration and consent forms to let us know what your decision is. If it helps, ask a friend or relative to fill in the forms for you. Please keep this information leaflet and a copy of the consent form for your records.

If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw or not to take part will not affect the standard of care you receive.

Thank you for taking time to read this information leaflet. Please keep it in a safe place for future reference

1	Your title	«PatTitle»
	Your first name	«PatForename»
	Your middle initials	«PatInitials»
	Your surname	«PatSurname»
	Your date of birth	«PatDOB»
	Your address	«PatAddress1»
		«PatAddress2»
		«PatAddress3» «PatCity»
	Postcode	«PatPostCode»
	Telephone number	«PatTelephone» <small>please supply if missing</small>
	email address	<small>please supply if missing</small>

2	Who is your next of kin?	<input type="text"/>																				
3	What is their telephone number?	<input type="text"/>																				
4	What is your marital status?	<input type="text"/>																				
5	Are you?	male <input type="checkbox"/> <small>go to 8</small> female <input type="checkbox"/> <small>go to 6</small>																				
6	Maiden name (if applicable)	<input type="text"/>																				
7	How many children have you had?	<input type="text"/>																				
8	Which hand do you write with?	Right <input type="checkbox"/> Left <input type="checkbox"/> Both <input type="checkbox"/>																				
9	What is your ethnic origin? <i>(please tick one)</i>	<table><tr><td>White</td><td><input type="checkbox"/></td><td>Pakistani</td><td><input type="checkbox"/></td></tr><tr><td>Black-Caribbean</td><td><input type="checkbox"/></td><td>Bangladeshi</td><td><input type="checkbox"/></td></tr><tr><td>Black-African</td><td><input type="checkbox"/></td><td>Chinese</td><td><input type="checkbox"/></td></tr><tr><td>Black-other</td><td><input type="checkbox"/></td><td>Indian</td><td><input type="checkbox"/></td></tr><tr><td>Other</td><td><input type="checkbox"/></td><td></td><td></td></tr></table>	White	<input type="checkbox"/>	Pakistani	<input type="checkbox"/>	Black-Caribbean	<input type="checkbox"/>	Bangladeshi	<input type="checkbox"/>	Black-African	<input type="checkbox"/>	Chinese	<input type="checkbox"/>	Black-other	<input type="checkbox"/>	Indian	<input type="checkbox"/>	Other	<input type="checkbox"/>		
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Other	<input type="checkbox"/>																					

Please go to page 2...

10 We have been told you have

«IVMType»

11 It was first diagnosed on

«PatDiagnosisDate»

12 You are looked after by

«collName»

at the following hospital

«CentreName»

13 Your General Practitioner is

«gpName»
«GPPracticeName»
«GPAddress1» «GPAddress2»
«GPCity» «GPPostCode»

14 Please list any other medical problems you may have

15 Please list any pills, tablets or other treatments you are taking

16 Has anyone in your family had a brain haemorrhage, epilepsy or an abnormal tangle of blood vessels in their brain like yours?

Please tick one box

Yes ☐

No ☐

17 Is there anything else that you think we should know, or that you would like to add?

13 March 2003

Department of Clinical Neurosciences
 Bramwell Dott Building
 Western General Hospital
 Crewe Road
 Edinburgh EH4 2XU
 tel/fax: 0131 537 2944
 e-mail: sivms@skull.dcn.ed.ac.uk
 web: <http://www.dcn.ed.ac.uk/ivm/>



«GPTitle» «GPForename» «GPSurname»
 «GPPracticeName»
 «GPAddress1»
 «GPAddress2»
 «GPCity» «GPPostCode»

Dear «GPTitle» «GPSurname»

Re. «name», «PatAddress1», «PatAddress2», «PatAddress3»
 «PatCity» «PatPostCode» Date of birth «PatDOB»

Thank you for replying to our annual questionnaire about «PatTitle» «PatSurname» on «LastOfAGReplyDate», in which you indicated that it is now appropriate for us to approach him for his consent to join the study, when it had not been in the past.

We are sorry to have to bother you about our study again, but we need your help to avoid "cold-calling" «PatTitle» «PatSurname» ourselves, yet obtain his consent to join our study to gain important information about the prognosis and treatment of his condition.

All we are asking you to do is to sign the enclosed letter from yourself to «PatTitle» «PatSurname», unless you wish to re-draft it, and post it with the enclosed package to her in the pre-paid envelope provided. The forms and pre-paid envelope are designed to make the task as easy and inexpensive for you as possible.

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Thank you in advance for your support.

Yours Sincerely

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

Prof. Charles P. Warlow
Professor of Medical Neurology

g:\trialdev\sivms\materials\enrollment\patient recruitment letter in the future.doc SIVMS No. «PatID»

«GPTitle» «GPForename» «GPSurname»
«GPPracticeName»
«GPAddress1»
«GPAddress2»
«GPCity» «GPPostCode»

13 March 2003

«name»
«PatAddress1»
«PatAddress2»
«PatAddress3»
«PatCity»
«PatPostCode»

Dear «PatTitle» «PatSurname»

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Please could you read the enclosed information leaflet, which gives further information about the study? If you are willing to take part, I would be very grateful if you would complete the consent form and SIVMS Questionnaire, and return them in the enclosed freepost envelope to the study team in Edinburgh as soon as you can. They would be very pleased if you took part so that we can all find out more about IVMs and how to manage them better.

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How can I obtain more information?

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For further information...

If you would like more information about any type of IVM, please contact us by telephone, fax, post or e-mail (details overleaf).

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Professor Peter Sandercock is available for independent advice about this study at the address overleaf, or by telephoning 0131 537 2928.

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Aberdeen

Mr DG Currie

Dundee

Dr RC Roberts

Edinburgh

Dr R Al-Shahi, Dr V Ritchie,

Dr RJ Sellar, Professor CP Warlow

Glasgow

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A register for people affected by vascular malformations of the brain in Scotland

Information leaflet

Version 2, May 2001

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. We hope you will join our study.

Why have I been chosen?

One of the doctors involved in your care has told us that you have a type of 'intracranial vascular malformation', or 'IVM'. An IVM is a tangle of blood vessels in your brain. The different types of IVM are:

- ◆ Arteriovenous malformation ('AVM')
- ◆ Cavernous malformation ('cavernoma' or 'cavernous angioma')
- ◆ Venous malformation ('venous anomaly')
- ◆ Dural arteriovenous fistula

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The aim of SIVMS is to find every person with an IVM in Scotland and enroll them in a confidential register. We only ask for a few minutes of your time each year.

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We are using the register to:

1. Find out how common IVMs are in Scotland
2. Find out what is important to you about having an IVM
3. Understand better the particular problems caused by IVMs over time

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What will happen if I take part?

After you register, we will extract some basic information about your medical history from your medical records. If you agree, we will also send you a short questionnaire asking some simple questions about your day-to-day life. This should take only 20 minutes to complete. We may occasionally need to telephone you.

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If English is not your first language, this leaflet could be translated for you

Will the information be confidential?

Any information collected about you will be kept strictly confidential and used only for this study. These details will only be available to research staff, and no-one else. The published results of the research will not identify individual people. We comply with the Data Protection Act 1998. We have full ethical approval for this study from the Multi-centre Research Ethics Committee for Scotland and your Local Research Ethics Committee.

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Do I have to take part?

It is up to you to decide whether or not to take part. Please complete and sign the enclosed registration and consent forms to let us know what your decision is. If it helps, ask a friend or relative to fill in the forms for you. Please keep this information leaflet and a copy of the consent form for your records.

If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw or not to take part will not affect the standard of care you receive.

Thank you for taking time to read this information leaflet. Please keep it in a safe place for future reference

«name»
«PatAddress1»
«PatAddress2»
«PatAddress3»
«PatCity» «PatPostCode»



SIVMS

consent form

	Please tick (✓) appropriate box	
	Yes	No
1. Have you read the information leaflet?	<input type="checkbox"/>	<input type="checkbox"/>
2. Has the leaflet given you enough information about the study?	<input type="checkbox"/>	<input type="checkbox"/>
3. Have you been offered an opportunity to ask questions and discuss this study (see leaflet)?	<input type="checkbox"/>	<input type="checkbox"/>
4. If so, have you received satisfactory answers to your questions?	<input type="checkbox"/>	<input type="checkbox"/>
5. Do you understand that participation is entirely voluntary?	<input type="checkbox"/>	<input type="checkbox"/>
6. Do you understand that you are free to withdraw from the study:		
at any time?	<input type="checkbox"/>	<input type="checkbox"/>
without having to give a reason for withdrawing?	<input type="checkbox"/>	<input type="checkbox"/>
without this affecting your future medical care?	<input type="checkbox"/>	<input type="checkbox"/>
Are you happy to receive a short questionnaire once a year?	<input type="checkbox"/>	<input type="checkbox"/>
Can we have access to your medical records, for the purposes of this study ONLY (we will respect confidentiality at ALL times)?	<input type="checkbox"/>	<input type="checkbox"/>

• Signature

_____Date

«name»day/month/year

Assent by another person (if you are unable to complete this form):

• Signature

_____Date

day/month/year

Name (capitals) _____

Relationship to the
person named above _____

1	Your title	«PatTitle»
	Your first name	«PatForename»
	Your middle initials	«PatInitials»
	Your surname	«PatSurname»
	Your date of birth	«PatDOB»
	Your address	«PatAddress1»
		«PatAddress2»
		«PatAddress3» «PatCity»
	Postcode	«PatPostCode»
	Telephone number	«PatTelephone» please supply if missing
	email address	please supply if missing

2	Who is your next of kin?																					
3	What is their telephone number?																					
4	What is your marital status?																					
5	Are you?	male <input type="checkbox"/> go to 8 female <input type="checkbox"/> go to 6																				
6	Maiden name (if applicable)																					
7	How many children have you had?	<input type="text"/>																				
8	Which hand do you write with?	Right <input type="checkbox"/> Left <input type="checkbox"/> Both <input type="checkbox"/>																				
9	What is your ethnic origin? (please tick one)	<table><tr><td>White</td><td><input type="checkbox"/></td><td>Pakistani</td><td><input type="checkbox"/></td></tr><tr><td>Black-Caribbean</td><td><input type="checkbox"/></td><td>Bangladeshi</td><td><input type="checkbox"/></td></tr><tr><td>Black-African</td><td><input type="checkbox"/></td><td>Chinese</td><td><input type="checkbox"/></td></tr><tr><td>Black-other</td><td><input type="checkbox"/></td><td>Indian</td><td><input type="checkbox"/></td></tr><tr><td>Other</td><td><input type="checkbox"/></td><td></td><td></td></tr></table>	White	<input type="checkbox"/>	Pakistani	<input type="checkbox"/>	Black-Caribbean	<input type="checkbox"/>	Bangladeshi	<input type="checkbox"/>	Black-African	<input type="checkbox"/>	Chinese	<input type="checkbox"/>	Black-other	<input type="checkbox"/>	Indian	<input type="checkbox"/>	Other	<input type="checkbox"/>		
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Black-other	<input type="checkbox"/>	Indian	<input type="checkbox"/>																			
Other	<input type="checkbox"/>																					

Please go to page 2...

10

We have been told you have

«IVMType»

11

It was first diagnosed on

«PatDiagnosisDate»

12

You are looked after by

«collName»

at the following hospital

«CentreName»

13

Your General Practitioner is

«gpName»

«GPPracticeName»

«GPAddress1» «GPAddress2»

«GPCity» «GPPostCode»

14

Please list any other medical problems you may have

15

Please list any pills, tablets or other treatments you are taking

16

Has anyone in your family had a brain haemorrhage, epilepsy or an abnormal tangle of blood vessels in their brain like yours?

Please tick one box

Yes

☐

No

☐

17

Is there anything else that you think we should know, or that you would like to add?

Department of Clinical Neurosciences
Bramwell Dott Building
Western General Hospital
Crewe Road
Edinburgh EH4 2XU
tel/fax: 0131 537 2944
e-mail: sivms@skull.dcn.ed.ac.uk
web: <http://www.dcn.ed.ac.uk/ivm/>



13 March 2003

«CollTitle» «CollForename» «CollInitials» «CollSurname»
«CentreName»
«CentreAddr1»
«CentreAddr2»
«CentreCity» «CentrePostCode»

Dear «CollTitle» «CollSurname»

Re. «name», «PatAddress1» «PatAddress2» «PatAddress3» «PatCity»
«PatPostCode»

Enrolment of your patient, «name», with SIVMS is now complete and her status in the study is as follows:

Type of intracranial vascular malformation	«IVMType»
Date of first diagnosis	«PatDiagnosisDate»
Access to GP records	No
Access to hospital records	No
Will «PatTitle» «PatSurname» receive questionnaires?	No

Thank you for your collaboration. Feel free to contact us if you have any questions or comments about the study.

Yours Sincerely,

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

Prof Charles P Warlow
Professor of Medical Neurology

g:\trialdev\sivms\materials\enrollment\gpconsultant patient enrolled.doc SIVMS «PatID»

Department of Clinical Neurosciences
Bramwell Dott Building
Western General Hospital
Crewe Road
Edinburgh EH4 2XU
tel/fax: 0131 537 2944
e-mail: sivms@skull.dcn.ed.ac.uk
web: <http://www.dcn.ed.ac.uk/ivm/>



13 March, 2003

«CollTitle» «CollForename» «CollInitials» «CollSurname»
«Department»
«CentreName»
«CentreAddr1»
«CentreAddr2»
«CentreCity» «CentrePostCode»

Dear «CollTitle» «CollSurname»

Re. «name», «PatAddress1» «PatAddress2» «PatAddress3», «PatCity»
«PatPostCode»

Although we are aware that «PatTitle» «PatSurname» died on «PatDeathDate», and we will not be attempting to contact any members of her family, we want to let you know that SIVMS holds data about her, and that her status in the study is as follows:

Type of intracranial vascular malformation	«IVMType»
Date of first diagnosis	«PatDiagnosisDate»
Date of death	«PatDeathDate»
Access to GP records?	No
Access to hospital records?	No
Will «PatTitle» «PatSurname» receive questionnaires?	No

Thank you for your collaboration. Feel free to contact us if you have any questions or comments about the study.

Yours Sincerely,

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

Prof Charles P Warlow
Professor of Medical Neurology

g:\trialdev\sivms\materials\enrollment\gpconsultant patient enrolled (dead).docSIVMS «PatID»

Department of Clinical Neurosciences
Bramwell Dott Building
Western General Hospital
Crewe Road
Edinburgh EH4 2XU
tel/fax: 0131 537 2944
e-mail: sivms@skull.dcn.ed.ac.uk
web: <http://www.dcn.ed.ac.uk/ivm/>



13 March 2003

«collName»
«Department»
«CentreName»
«CentreAddr1»
«CentreAddr2»
«CentreCity»
«CentreRegion» «CentrePostCode»

Dear «CollTitle» «CollSurname»

Re. «patientName»
«PatAddress1» «PatAddress2» «PatAddress3» «PatCity» «PatDistrict»
«PatPostCode»

Enrolment of your patient, «PatTitle» «PatSurname», with SIVMS is now complete and her status in the study is as follows:

Type of intracranial vascular malformation	IVM type
	IVM type
Date of first diagnosis	Date
Access to GP records	«PatGPRRecordsConsent»
Access to hospital records	«RegNotesAccess»
Will «PatTitle» «PatSurname» receive questionnaires?	«PatQConsent»

Thank you for your collaboration. Feel free to contact us if you have any questions or comments about the study.

Yours Sincerely,

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

Prof Charles P Warlow
Professor of Medical Neurology

g:\trialdev\sivms\materials\enrollment\gpconsultant patient enrolled changed.doc SIVMS 267

Department of Clinical Neurosciences
 Bramwell Dott Building
 Western General Hospital
 Crewe Road
 Edinburgh EH4 2XU
 tel/fax: 0131 537 2944
 e-mail: sivms@skull.dcn.ed.ac.uk
 web: <http://www.dcn.ed.ac.uk/ivm/>



13 March 2003

«gpName»
 «GPPracticeName»
 «GPAddress1»
 «GPAddress2»
 «GPCity» «GPPostCode»

Dear «GPTitle» «GPSurname»

Re. «patientName»
 «PatAddress1» «PatAddress2» «PatAddress3» «PatCity» «PatPostCode»

We are writing to request copies of «patientName»'s case-notes. She is enrolled with the Scottish Intracranial Vascular Malformation Study, and you previously indicated that you would be happy for us to have access to her GP notes.

We would be very grateful if you could now send us copies of the following:

- a) your referral letter(s) and hospital clinic letters relevant to «patientName»'s IVM
- b) discharge summaries relevant to «patientName»'s IVM
- c) reports of brain imaging
- d) a computerised diagnostic summary sheet, if your practice produces them

We **do not** require copies of our own letters or forms that we have sent to you.

If your practice staff cannot provide these copies or there is a charge for providing them, we would be very happy to discuss with them how best to arrange for copies to be made, perhaps by sending the notes to us. Would you please attach the enclosed label to the front of «PatTitle» «PatSurname»'s practice notes to ensure they are not destroyed, as SIVMS is a long-term study and we hope to follow-up the patients for many years, possibly decades. We enclose a freepost envelope for your reply.

Yours Sincerely

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

Prof Charles P Warlow
Professor of Medical Neurology

g:\trialdev\sivms\medical records\gpcasenotesrequestletter (alive).doc SIVMS No.«PatID»

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13 March, 2003

Practitioner Services Manager
 Practitioner Services

Dear «Practitioner Services Manager»

Re: «Patient_Name», née Maiden Name
«PatAddress1» «PatAddress2» «PatAddress3», «PatCity» «PatPostCode»
 Date of birth «PatDOB», Date of death «PatDeathDate»
 under the care of «GPTitle» «GPForename» «GPIinitials» «GPSurname»
 at «GPPPracticeName»

We are writing to request copies of «PatTitle» «PatSurname»'s notes, because she is registered with the Scottish Intracranial Vascular Malformation Study. Although she is dead, it is important that we collect information from her notes. Please could we have copies of any clinic letters, discharge summaries and reports of brain imaging that have been produced since we last requested them on «PatGPDateNotesRequested». Please attach the enclosed label to the front of her case-notes to prevent them from being destroyed, as SIVMS is a long-term study.

We enclose a copy of approval given by her GP, allowing us to gain access to her case-notes. We also enclose a copy of the study protocol and copies of approval for our study's methods from the Multi-Centre Research Ethics Committee for Scotland and your Local Research Ethics Committee.

Many Thanks,

Yours Sincerely,

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

Prof Charles P Warlow
Professor of Medical Neurology

g:\trialdev\sivms\medical records\gpcasenotesrequestletter (deceased).doc SIVMS No. «PatID»

Department of Clinical Neurosciences
 Bramwell Dott Building
 Western General Hospital
 Crewe Road
 Edinburgh EH4 2XU
 tel/fax: 0131 537 2944
 e-mail: sivms@skull.dcn.ed.ac.uk
 web: <http://www.dcn.ed.ac.uk/ivm/>



13 March, 2003

«CentreMedicalRecordsManagerTitle»
 «CentreName»
 «CentreAddr1»
 «CentreAddr2»
 «CentreCity»
 «CentreRegion»
 «CentrePostCode»

Dear «CentreMedicalRecordsManager»

Re: «patientName», «PatAddress1» «PatAddress2» «PatAddress3» «PatCity»
 «PatDistrict» «PatPostCode»
 Date of birth «PatDOB»
 Hospital No. «RegHospitalNo»
 under the care of «colIname»

We are writing to request copies of the case-notes for «PatTitle» «PatSurname», who is enrolled with the Scottish Intracranial Vascular Malformation Study. Please could we have copies of:

- clinic letters and discharge summaries from the correspondence section
- neuroradiology and neuropathology reports from the investigation section

Please attach the enclosed label to the front of the patient's case-notes to prevent them from being destroyed, as SIVMS is a long-term study.

We enclose a copy of the approval from the patient's consultant, allowing us to gain access to the case-notes. If you wish, we would be happy to send you a copy of the study protocol and copies of approval for our study's methods from the Multi-Centre Research Committee for Scotland and your Local Research Ethics Committee.

Many Thanks,

Yours Sincerely,

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

Prof Charles P Warlow
Professor of Medical Neurology

g:\trialdev\sivms\medical records\hospitalcasenotesrequestletter (dead or alive).doc SIVMS No.«PatID»

Department of Clinical Neurosciences
 Bramwell Dott Building
 Western General Hospital
 Crewe Road
 Edinburgh EH4 2XU
 tel/fax: 0131 537 2944
 e-mail: sivms@skull.dcn.ed.ac.uk
 web: <http://www.dcn.ed.ac.uk/ivm/>



13 March, 2003

«CentreMedicalRecordsManagerTitle»
 «CentreName»
 «CentreAddr1»
 «CentreAddr2»
 «CentreCity»
 «CentreRegion»
 «CentrePostCode»

Dear «CentreMedicalRecordsManager»

Re: «patientName», «PatAddress1» «PatAddress2» «PatAddress3» «PatCity»
 «PatDistrict» «PatPostCode»
 Date of birth «PatDOB», Date of death «PatDeathDate»
 Hospital No. Unknown«RegHospitalNo»
 under the care of «collname»

We are writing to request copies of the case-notes for «PatTitle» «PatSurname», who is enrolled with the Scottish Intracranial Vascular Malformation Study. Please could we have copies, , of:

- clinic letters and discharge summaries from the correspondence section
- neuroradiology and neuropathology reports from the investigation section

We enclose a copy of the approval from the patient's consultant, allowing us to gain access to the case-notes. Please attach the enclosed label to the front of the patient's case-notes to prevent them from being destroyed, as SIVMS is a long-term study. If you wish, we would be happy to send you a copy of the study protocol and copies of approval for our study's methods from the Multi-Centre Research Committee for Scotland and your Local Research Ethics Committee.

Many Thanks,

Yours Sincerely,

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

Prof Charles P Warlow
Professor of Medical Neurology

g:\trialdev\sivms\medical records\hospitalcasenotesrequestletter (dead).doc SIVMS No. «PatID»

Department of Clinical Neurosciences
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 Crewe Road
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 tel/fax: 0131 537 2944
 e-mail: sivms@skull.dcn.ed.ac.uk
 web: <http://www.dcn.ed.ac.uk/ivm/>



13 March, 2003

«GPTitle» «GPForename» «GPInitials» «GPSurname»
 «GPPracticeName»
 «GPAddress1»
 «GPAddress2»
 «GPCity» «GPPostCode»

Dear «GPTitle» «GPSurname»

**Re. «PatTitle» «PatForename» «PatInitials» «PatSurname»
 «PatAddress1» «PatAddress2» «PatAddress3» «PatCity» «PatPostCode»**

It is now approximately one year since we last checked «PatTitle» «PatSurname»'s participation in the Scottish Intracranial Vascular Malformation Study (SIVMS). Although we do follow-up «PatTitle» «PatSurname» through her hospital notes, there is vital follow-up information that only you will be able to help us with.

For this reason, we have also enclosed a letter asking for copies of recent records held in her GP notes relating to this follow-up information.

We would therefore be very grateful if you could please check the details on the attached sheet and return the seven-step form with the relevant copies of her GP notes, if appropriate, to us in the freepost envelope provided.

We enclose a pad of post-its and a yearly GP newsletter, as a small token of our gratitude to you for helping with the study.

Yours Sincerely

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

Prof Charles P Warlow
Professor of Medical Neurology

g:\trialdev\sivms\materials\followup\gp annual letter noq.doc SIVMS No.«PatID»

Patient name	«PatTitle» «PatForename» «PatInitials» «PatSurname»
--------------	---

Date of birth «PatDOB»

Patient address	«PatAddress1», «PatAddress2» «PatAddress3» «PatCity» «PatPostCode»
------------------------	---

Please tick (✓) appropriate box

Yes	No
-----	----

Is «PatTitle» «PatSurname» still alive?
If you answered 'No', please tell us her date of death:

11

Is her address the same (as above)?
If you answered 'No', please amend the address.

11

Recently, it has not been appropriate to contact «PatTitle» «PatSurname» by post. Should we now send her Another consent pack (we did so before) If you answered 'No', please comment:

11

Has «PatTitle» «PatSurname» been seen about her intracranial vascular malformation in hospital in the last year?
If you answered 'Yes', please fill in this section:

☐ ☐

Approximate
date of hospital
visit / stay

Which hospital?

Consultant
(if known)

Reason for appointment / admission

please continue overleaf if necessary

If not already mentioned in ④, has «PatTitle» «PatSurname» suffered from the following in the last year (giving date(s) where applicable)?

Brain haemorrhage(s)

Yes / No

day/month/year

Epilepsy

Yes / No

day/month/year

Which of these best describes «PatTitle» «PatSurname»'s *current* state?

No symptoms ☐

Minor symptoms, which do not interfere with her lifestyle ☐

Some restrictions to her lifestyle, but she looks after herself ☐

Significant restriction to lifestyle, preventing total independence ☐

Severe handicap preventing independent existence, but not requiring constant attention ☐

Severe handicap, totally dependent, requiring attention night and day ☐

Signature

Date _____

day/month/year

«GPTitle» «GPSurname»

«GPPPracticeName», «GPAddress1», «GPAddress2»

«GPCity» «GPPostCode»

Department of Clinical Neurosciences
Bramwell Dott Building
Western General Hospital
Crewe Road
Edinburgh EH4 2XU
tel/fax: 0131 537 2944
e-mail: sivms@skull.dcn.ed.ac.uk
web: <http://www.dcn.ed.ac.uk/ivm/>



13 March, 2003

«GPTitle» «GPForename» «GPInitials» «GPSurname»
«GPPracticeName»
«GPAddress1»
«GPAddress2»
«GPCity» «GPPostCode»

Dear «GPTitle» «GPSurname»

Re. «PatTitle» «PatForename» «PatInitials» «PatSurname»
«PatAddress1» «PatAddress2» «PatAddress3» «PatCity» «PatPostCode»

It is now approximately one year since «PatTitle» «PatSurname» was last contacted about the Scottish Intracranial Vascular Malformation Study (SIVMS).

Because we are about to send him a follow-up questionnaire, we would be very grateful to you for checking the details on the attached sheet. Although we do follow-up «PatTitle» «PatSurname» through his hospital notes, there is vital follow-up information that only you will be able to help us with.

For this reason, we have also enclosed a letter asking for copies of recent records held in his GP notes relating to this follow-up information.

We would therefore be very grateful if you could please check the details on the attached sheet and return the seven-step form with the relevant copies of his GP notes, if appropriate, to us in the freepost envelope provided.

We enclose a pad of post-its and a yearly GP newsletter, as a small token of our gratitude to you for helping with the study.

Yours Sincerely

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

Prof Charles P Warlow
Professor of Medical Neurology

g:\trialdev\sivms\materials\followup\gp annual letter q.doc SIVMS No.«PatID»

Patient name «PatTitle» «PatForename» «PatInitials» «PatSurname»
Date of birth «PatDOB»
Patient address «PatAddress1», «PatAddress2»
«PatAddress3» «PatCity» «PatPostCode»

	Please tick (✓) appropriate box	
	Yes	No
Is «PatTitle» «PatSurname» still alive? If you answered 'No', please tell us his date of death:	<input type="checkbox"/>	<input type="checkbox"/>
Is his address the same (as above)? If you answered 'No', please amend the address.	<input type="checkbox"/>	<input type="checkbox"/>
«PatTitle» «PatSurname» agreed to complete an annual questionnaire. Is it still appropriate to send him a questionnaire? If you answered 'No', please comment:	<input type="checkbox"/>	<input type="checkbox"/>
Has «PatTitle» «PatSurname» been seen about his intracranial vascular malformation in hospital in the last year? If you answered 'Yes', please fill in this section:	<input type="checkbox"/>	<input type="checkbox"/>

Approximate date of hospital visit / stay	Which hospital?	Consultant (if known)	Reason for appointment / admission
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____

please continue overleaf if necessary

If not already mentioned in ④, has «PatTitle» «PatSurname» suffered
from the following in the last year (giving date(s) where applicable)?

Brain haemorrhage(s)	Yes / No	_____
		day/month/year
Epilepsy	Yes / No	_____
		day/month/year

Which of these best describes «PatTitle» «PatSurname»'s *current* state?

No symptoms	<input type="checkbox"/>
Minor symptoms, which do not interfere with his lifestyle	<input type="checkbox"/>
Some restrictions to his lifestyle, but he looks after himself	<input type="checkbox"/>
Significant restriction to lifestyle, preventing total independence	<input type="checkbox"/>
Severe handicap preventing independent existence, but not requiring constant attention	<input type="checkbox"/>
Severe handicap, totally dependent, requiring attention night and day	<input type="checkbox"/>

Signature	_____	Date	_____
			day/month/year
	«GPTitle» «GPSurname»		
	«GPPracticeName»		
	«GPAddress1», «GPAddress2»		
	«GPCity» «GPPostCode»		

Department of Clinical Neurosciences
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 web: <http://www.dcn.ed.ac.uk/ivm/>



13 March, 2003

«GPTitle» «GPForename» «GPSurname»
 «GPPPracticeName»
 «GPAddress1»
 «GPAddress2»
 «GPCity» «GPPostCode»

Dear «GPTitle» «GPSurname»

Re. «patientName» «PatMaidenName»
 «PatAddress1» «PatAddress2» «PatAddress3» «PatCity» «PatPostCode»

We last wrote to request copies of «PatTitle» «PatSurname»'s case-notes on «PatGPDateNotesRequested». He is enrolled with the Scottish Intracranial Vascular Malformation Study, and you previously indicated that you would be happy for us to copy his GP notes.

We would be very grateful if you could now send us copies of correspondence **since «DateofLastCorrespondence»**, *especially* relating to clinically significant events that you mentioned on the enclosed follow-up questionnaire. We would like copies of the following that have been produced since «DateofLastCorrespondence»:

- a) your referral letter(s) and hospital clinic letters relevant to «PatTitle» «PatSurname»'s IVM
- b) discharge summaries relevant to «PatTitle» «PatSurname»'s IVM
- c) reports of brain imaging
- d) a diagnostic summary sheet, if your practice produces them

We **do not** require copies of our own letters that we have sent to you. Please let us know if there is **not** a sticker on the front of the notes indicating that «PatTitle» «PatSurname» is included in this study, and we will send you one.

If your practice staff cannot provide these copies or there is a charge for providing them, we would be very happy to discuss with them how best to arrange for copies to be made and/or charged for, perhaps by sending the notes to us. We enclose a freepost envelope for your reply.

Yours Sincerely

Dr Rustam Al-Shahi
 MRC Clinical Training Fellow

Prof Charles P Warlow
 Professor of Medical Neurology

d:\data\s.i.v.m.s\writing\thesis\sivms letters\annualgpccasenotesrequestletter(alive).doc SIVMS No.«PatID»

Department of Clinical Neurosciences
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 tel/fax: 0131 537 2944
 e-mail: sivms@skull.dcn.ed.ac.uk
 web: <http://www.dcn.ed.ac.uk/ivm/>



13 March, 2003

«CentreMedicalRecordsManagerTitle»
 «CentreName»
 «CentreAddr1»
 «CentreAddr2»
 «CentreCity» «CentrePostCode»

Dear «CentreMedicalRecordsManager»

Re: «patientName», «PatAddress1» «PatAddress2» «PatAddress3» «PatCity»
 «PatDistrict» «PatPostCode»
 Date of birth «PatDOB»
 Hospital No. «RegHospitalNo»
 under the care of «collname»

«PatForename» «PatSurname» is enrolled with the Scottish Intracranial Vascular Malformation Study, and it is now one year since we last requested copies of his case-notes. Please could we have copies, that have been produced since «RegDateOfLastCorrespondance», of:

- clinic letters and discharge summaries from the correspondence section
- neuroradiology and neuropathology reports from the investigation section

If there is **not** a sticker on the front of the notes indicating his enrolment with our study, please let us know and we will send you one.

Many Thanks,

Yours Sincerely,

Dr Rustam Al-Shahi
 MRC Clinical Training Fellow

Prof Charles P Warlow
 Professor of Medical Neurology

d:\data\s.i.v.m.s\writing\thesis\sivms letters\annualhospitalcasenotesrequestletter.doc SIVMS No.«PatID»

Department of Clinical Neurosciences
 Bramwell Dott Building
 Western General Hospital
 Crewe Road
 Edinburgh EH4 2XU
 tel/fax: 0131 537 2944
 e-mail: sivms@skull.dcn.ed.ac.uk
 web: <http://www.dcn.ed.ac.uk/ivm/>



13 March 2003

«PatTitle» «PatForename» «PatInitials» «PatSurname»
 «PatAddress1»
 «PatAddress2»
 «PatAddress3»
 «PatCity» «PatDistrict» «PatPostCode»

Dear «PatTitle» «PatSurname»,

Thank you very much indeed for agreeing to participate in the Scottish Intracranial Vascular Malformation Study (SIVMS). We are grateful for your response to the short enrollment questionnaire we sent you on «PatEnrDateSent».

We would like you to tell us how you are getting on by completing the enclosed yearly questionnaire that asks some questions about your daily activities and your health. Your answers are extremely valuable to us, so please take some time to complete the questionnaire carefully. We anticipate it will take between 20 and 30 minutes to complete. Do ask a relative or friend to help you if you cannot complete the questionnaire. As we mentioned in the information leaflet, your confidentiality is respected at all times.

When you have completed the questionnaire, please return it in the enclosed freepost envelope as soon as you can. Do not hesitate to contact us if you require any information about the questionnaire, help with its completion or further information. To keep you up-to-date with the study, we have enclosed a yearly participant newsletter.

Thank you in advance for your support.

Yours Sincerely,

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

Prof. Charles P. Warlow
Professor of Medical Neurology

g:\trialdev\sivms\materials\followup\patient questionnaire letter.doc SIVMS No.«PatID»

SIVMS Yearly Questionnaire

Your Title	«PatTitle»
Your First Name	«PatForename»
Your Middle Initials	«PatInitials»
Your Surname	«PatSurname»
Your Address	«PatAddress1»
	«PatAddress2» «PatAddress3»
	«PatCity» «PatDistrict»
Post Code	«PatPostCode»
Telephone number	«PatTelephone»
SIVMS number	«PatID»

Please correct your details, if necessary

Instructions for completing the questionnaire

1. Please answer every question.
2. Some questions may look a bit like others, but each one is different.
3. Please take time to read each question carefully, and tick the box next to the answer that is closest to the way you feel.
4. Ask a friend or relative for help if you need it.
5. Return your completed questionnaire in the freepost envelope provided.
6. Please turn the page and begin answering the questions now.

1. Please read the following descriptions from people who have had similar medical problems to you and choose *one* which best describes your *present* state:

Tick one box:

- I have no problems at all and cope well with life. ☐
- I have a few symptoms but these do not interfere with my everyday life. ☐
- I have symptoms which have caused some changes in my life, but I am still able to look after myself. ☐
- I have symptoms which have significantly changed my life and prevent me from coping fully, *and* I need some help with looking after myself. ☐
- I have quite severe symptoms which mean I need to have help from other people, but I am not so bad as to need attention day and night. ☐
- I have major symptoms which severely handicap me and I need constant attention day and night. ☐

2. In general would you say your health is:

Tick one box:

- Excellent ☐
- Very good ☐
- Good ☐
- Fair ☐
- Poor ☐

3. Compared to one year ago, how would you rate your health in general *now*?

Tick one box:

- Much better than one year ago ☐
- Somewhat better than one year ago ☐
- About the same ☐
- Somewhat worse now than one year ago ☐
- Much worse now than one year ago ☐

4. The following questions are about activities you might do during a typical day. Does *your health now* limit you in these activities?

Tick one box on each line

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a) Vigorous activities, <i>such as running, lifting heavy objects, participating in strenuous sports</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b) Moderate activities, <i>such as moving a table, pushing a vacuum cleaner, bowling or playing golf</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c) Lifting or carrying groceries	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d) Climbing several flights of stairs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
e) Climbing one flight of stairs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
f) Bending, kneeling or stooping	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
g) Walking more than a mile	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
h) Walking half a mile	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
i) Walking 100 yards	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
j) Bathing and dressing yourself	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

5. During the *past 4 weeks*, have you had any of the following problems with your work or other regular daily activities *as a result of your physical health*?

Tick one box on each line

	Yes	No
Cut down on the amount of time you spent on work or other activities	<input type="checkbox"/>	<input type="checkbox"/>
Accomplished less than you would like	<input type="checkbox"/>	<input type="checkbox"/>
Were limited in the kind of work or other activities	<input type="checkbox"/>	<input type="checkbox"/>
Had difficulty performing the work or other activities (for example, it took extra effort)	<input type="checkbox"/>	<input type="checkbox"/>

6. During the *past 4 weeks*, have you had any of the following problems with your work or other regular daily activities *as a result of any emotional problems* (such as feeling depressed or anxious)?

Tick one box on each line

Yes No

Cut down on the **amount of time** you spent on work or other activities ☐ ☐

Accomplished less than you would like ☐ ☐

Didn't do work or other activities as **carefully** as usual ☐ ☐

7. During the *past 4 weeks*, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

Tick one box:

Not at all ☐

Slightly ☐

Moderately ☐

Quite a bit ☐

Extremely ☐

8. How much *bodily* pain have you had during the *past 4 weeks*?

Tick one box:

None ☐

Very mild ☐

Mild ☐

Moderate ☐

Severe ☐

Very severe ☐

9. During the *past 4 weeks*, how much did *pain* interfere with your normal work (both outside the home and housework)?

Tick one box:

Not at all ☐

A little bit ☐

Moderately ☐

Quite a bit ☐

Extremely ☐

10. These questions are about how you feel and how things have been with you *during the past 4 weeks*. For each question please indicate the one answer that comes closest to the way you have been feeling. How much during the *past 4 weeks*:

Tick one box on each line

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a) Did you feel full of life?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b) Have you been a very nervous person?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c) Have you felt so down in the dumps that nothing could cheer you up?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d) Have you felt calm and peaceful?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
e) Did you have a lot of energy?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
f) Have you felt downhearted and low?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
g) Did you feel worn out?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
h) Have you been a happy person?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
i) Did you feel tired?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

11. During the past 4 weeks, how much of the time has your *physical health or emotional problems* interfered with your social activities (like visiting friends or close relatives)?

Tick one box:

All of the time ☐

Most of the time ☐

A good bit of the time ☐

Some of the time ☐

A little of the time ☐

None of the time ☐

12. How TRUE or FALSE is *each* of the following statements for you:

Tick one box on each line

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
I seem to get ill more easily than other people	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am as healthy as anybody I know	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I expect my health to get worse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
My health is excellent	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

13. In the *past week* did you have full control of your bowels most days?
- Tick one box:
- Yes ☐
- No, I have occasional accidents (once a week) ☐
- No, I am incontinent or need help with an enema ☐

14. In the *past week* did you have full control of your bladder most days?
- Tick one box:
- Yes ☐
- No, I have occasional accidents (less than once a day) ☐
- No, I am incontinent (or use a catheter) ☐

15. In the last *two days* did you manage to clean your teeth, brush your hair or shave without help?
- Tick one box:
- Yes ☐
- No, I need help ☐

16. In the past *two weeks* could you use the toilet (or commode) without help from another person?
- Tick one box:
- Yes, I am independent ☐
- No, I need minor assistance ☐
- No, I need quite a lot of help ☐

- 17. In the last *two weeks* did you need help from another person to eat meals?**

Tick one box:

No, I am independent ☐Yes, I need some help ☐Yes, I need quite a lot of help ☐

- 18. In the past *two weeks* did you need help from another person to get out of bed or up from a chair?**

Tick one box:

No, I am totally independent ☐Yes, I need minimal help ☐Yes, I can sit unaided, but I need help to transfer ☐Yes, I am unable to transfer ☐

- 19. In the past *two weeks* did you need help from another person with walking?**

Tick one box:

No, I am independent for at least 50 yards ☐Yes, I can walk 50 yards with help ☐I am independent in a wheelchair for 50 yards ☐Yes, I am immobile ☐

- 20. In the last *two weeks* did you need help from another person to dress and undress?**

Tick one box:

No, I am independent ☐Yes, I need help with *some* things ☐Yes, I need help with *most* things ☐

- 21. In the past *two weeks* did you need help from another person to climb stairs?**

Tick one box:

No, I am independent ☐Yes, I need physical help or verbal support ☐I am unable ☐

22. In the last *two weeks* did you manage to have a bath, shower or wash all over without help?

Tick one box:

Yes ☐No, I need help ☐

23. I feel tense or 'wound up':

Tick one box:

Most of the time ☐A lot of the time ☐From time to time, occasionally ☐Not at all ☐

24. I still enjoy the things I used to enjoy:

Tick one box:

Definitely as much ☐Not quite so much ☐Only a little ☐Hardly at all ☐

25. I get a sort of frightened feeling as if something awful is about to happen:

Tick one box:

Very definitely and quite badly ☐Yes, but not too badly ☐A little, but it doesn't worry me ☐Not at all ☐

26. I can laugh and see the funny side of things:

Tick one box:

As much as I always could ☐Not quite so much now ☐Definitely not so much now ☐Not at all ☐

27. Worrying thoughts go through my mind:

Tick one box:

A great deal of the time ☐

A lot of the time ☐

From time to time, but not too often ☐

Only occasionally ☐

28. I feel cheerful

Tick one box:

Not at all ☐

Not often ☐

Sometimes ☐

Most of the time ☐

29. I can sit at ease and feel relaxed:

Tick one box:

Definitely ☐

Usually ☐

Not often ☐

Not at all ☐

30. I feel as if I am slowed down:

Tick one box:

Nearly all the time ☐

Very often ☐

Sometimes ☐

Not at all ☐

31. I get a sort of frightened feeling like “butterflies” in the stomach:

Tick one box:

Not at all ☐

Occasionally ☐

Quite often ☐

Very often ☐

32. I have lost interest in my appearance:

Tick one box:

Definitely ☐I don't take as much care as I should ☐I may not take quite as much care ☐I take just as much care as ever ☐**33. I feel restless as if I have to be on the move:**

Tick one box:

Very much indeed ☐Quite a lot ☐Not very much ☐Not at all ☐**34. I look forward with enjoyment to things:**

Tick one box:

As much as I ever did ☐Rather less than I used to ☐Definitely less than I used to ☐Hardly at all ☐**35. I get sudden feelings of panic:**

Tick one box:

Very often indeed ☐Quite often ☐Not very often ☐Not at all ☐**36. I can enjoy a good book or radio or TV programme:**

Tick one box:

Often ☐Sometimes ☐Not often ☐Very seldom ☐

37. Do you have nose bleeds?Yes ☐ If 'Yes' go to question 38No ☐ If 'No' go to question 40**38. At what age did they start?****39. How often do you have nosebleeds?**

Tick one box:

Rarely ☐Every month ☐Every week ☐Daily ☐More often ☐**40. Do you have any red spots on your lips, tongue or fingers?**Yes ☐ If 'Yes' go to question 41No ☐ If 'No' go to question 43**41. How many red spots do you have?****42. Where are these red spots?****43. Are you now, or have you ever been, significantly bothered by recurrent headaches?**

Tick one box:

Yes ☐No ☐**44. Do you have epilepsy ('seizures' or 'fits')?**We will **not** disclose the answer you give to this question to the Driving Vehicle Licensing AuthorityYes ☐No ☐

45. Who completed this questionnaire?☐ You☐ Someone else...

Please state name and relationship to the person
named on the front of this form:

**46. Signature of the person
completing this questionnaire:****Date of completion:****47. Please add any comments below:****48. Please return this questionnaire to us in the freepost envelope.**

THANK YOU FOR YOUR HELP!

Department of Clinical Neurosciences
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Crewe Road
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tel/fax: 0131 537 2944
e-mail: sivms@skull.dcn.ed.ac.uk
web: <http://www.dcn.ed.ac.uk/ivm/>



13 March, 2003

«Name»
«PatAddress1»
«PatAddress2»
«PatAddress3»
«PatCity»
«PatPostCode»

Dear «PatTitle» «PatSurname»,

Thank you very much indeed for completing your yearly SIVMS questionnaire on «QCompletionDate».

In the questionnaire you mentioned that you had suffered from epilepsy, seizures or fits. Could you kindly complete the enclosed additional, small questionnaire to give us a little more information about them? We will not be bothering you with any other questionnaires until next year!

When you have completed the questionnaire, please return it in the enclosed freepost envelope as soon as you can. Do not hesitate to contact us if you require any information about the questionnaire, help with its completion or further information.

Thank you in advance for your support.

Yours Sincerely,

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

Prof. Charles P. Warlow
Professor of Medical Neurology

g:\trialdev\sivms\materials\followup\patient epilepsy questionnaire letter.doc SIVMS No. «PatID»

SIVMS Epilepsy Questionnaire

Your Title	«PatTitle»
Your First Name	«PatForename»
Your Middle Initials	«PatInitials»
Your Surname	«PatSurname»
Your Address	«PatAddress1»
	«PatAddress2»
	«PatAddress3» «PatCity»
Post Code	«PatPostCode»
Telephone number	«PatTelephone»
SIVMS No.	«PatID»

Please correct your details, if necessary

Instructions for completing the questionnaire

1. Please answer every question.
2. Some questions may look a bit like others, but each one is different.
3. Please take time to read each question carefully, and tick the box next to the answer that is closest to the way you feel.
4. Ask a friend or relative for help if you need it.
5. Return your completed questionnaire in the freepost envelope provided.
6. Please turn the page and begin answering the questions now.

1. Below are some descriptions of different kinds of epileptic attacks. Which of these descriptions matches the attacks you have?

Please tick all the boxes that apply to you

'Grand mal' attacks. Unconsciousness with the body becoming stiff with jerking of all the limbs, and frothing at the mouth, possibly with difficulty breathing. Followed by a period of sleepiness and confusion lasting for at least 5 minutes before a full recovery. ☐

'Petit mal' attacks. A brief episode of no more than a few seconds with blankness without falling and possibly flickering of the eyelids. ☐

Attacks with a trance-like state, sometimes with lip-smacking, swallowing, gesturing or fidgeting, followed by confusion, usually with at least a minute before full recovery. ☐

Attacks of falling with a brief loss of consciousness preceded by a feeling of light-headedness which comes on gradually, but which may be followed by sweating and clamminess, shakiness and sickness ☐

Brief jerks of the arms and body (sometimes the legs) occurring usually within an hour or two of waking without any blackout ☐

Some other kind of attack ☐
please describe below

2. Do your attacks happen:

Please tick one box

Only while you are asleep ☐

Only while you are awake ☐

At any time of day or night ☐

3. How old were you when you had your *first* epileptic attack?

years

4. When did you have your *last* attack?

Please give the date

/ /

5. How many epileptic attacks have you had *in the past year*?

Please tick one box

None ☐Less than one per month ☐One or more per month ☐**6. Who completed this questionnaire?**☐ You☐ Someone else...Please state name and relationship to the person
named on the front of this form:**7. Signature of the person
completing this questionnaire:****Date of completion:****8. Please return this questionnaire to us in the freepost envelope.****THANK YOU FOR YOUR HELP!**

Department of Clinical Neurosciences
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tel/fax: 0131 537 2944
e-mail: sivms@skull.dcn.ed.ac.uk
web: <http://www.dcn.ed.ac.uk/ivm/>



13 March, 2003

«Name»
«PatAddress1»
«PatAddress2»
«PatAddress3»
«PatCity»
«PatPostCode»

Dear «PatTitle» «PatSurname»

Thank you very much indeed for completing your yearly SIVMS questionnaire on «QCompletionDate».

In the questionnaire you mentioned that you had suffered from headaches. Could you kindly complete the enclosed additional, small questionnaire to give us a little more information about them? We will not be bothering you with any other questionnaires until next year!

When you have completed the questionnaire, please return it in the enclosed freepost envelope as soon as you can. Do not hesitate to contact us if you require any information about the questionnaire, help with its completion or further information.

Thank you in advance for your support.

Yours Sincerely,

Dr Rustam Al-Shahi
MRC Clinical Training Fellow

Prof. Charles P. Warlow
Professor of Medical Neurology

g:\trialdev\sivms\materials\followup\patient headache questionnaire letter.doc SIVMS No. «PatID»

SIVMS Headache Questionnaire

Your Title	«PatTitle»
Your First Name	«PatForename»
Your Middle Initials	«PatInitials»
Your Surname	«PatSurname»
Your Address	«PatAddress1»
	«PatAddress2»
	«PatAddress3» «PatCity»
Post Code	«PatPostCode»
Telephone number	«PatTelephone»
SIVMS No.	«PatID»

Please correct your details, if necessary

Instructions for completing the questionnaire

1. Please answer every question.
2. Some questions may look a bit like others, but each one is different.
3. Please take time to read each question carefully, and tick the box next to the answer that is closest to the way you feel.
4. Ask a friend or relative for help if you need it.
5. Return your completed questionnaire in the freepost envelope provided.
6. Please turn the page and begin answering the questions now.

1. How often have you had headaches *in the past year*?

Please tick one box

Never ☐Less than once per month ☐Once or more per month ☐**2. Have you had at least 5 separate attacks of headache severe enough to require that you stop or decrease your activities or take a medication for pain?**

Tick one box:

Yes ☐No ☐

If 'No' stop here.

3. Do you have headache-free intervals of days to weeks between severe headache attacks?

Tick one box:

Yes ☐No ☐**4. Do your headache attacks usually last more than four hours and less than three days?**

Tick one box:

Yes ☐No ☐

If 'No' stop here.

5. Are your most bothersome headaches:

Tick one box on each line

Yes NoOften pulsating ('throbbing')? ☐ ☐Often on one side of the head, for at least a portion of the headache attack? ☐ ☐Severe enough to make you stop or decrease your activities? ☐ ☐Made worse by physical activity? ☐ ☐

6. Are your headache attacks accompanied by:

Tick one box on each line

	Yes	No
Nausea or vomiting?	<input type="checkbox"/>	<input type="checkbox"/>
Sensitivity to light?	<input type="checkbox"/>	<input type="checkbox"/>
Sensitivity to noise?	<input type="checkbox"/>	<input type="checkbox"/>

7. With *at least 2* of your headache attacks have you had temporary visual disturbance (for example, shimmering lights, zigzags, blind spots, circles, crescent shapes) just before or during the headache?

Tick one box:

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>

If 'No' go to question 13

8. Which of the following best describes your visual disturbance:

Tick one box:

Silver streaks	<input type="checkbox"/>	Heat waves	<input type="checkbox"/>
White lights	<input type="checkbox"/>	Flashing gold lights	<input type="checkbox"/>
Light objects appearing excessively bright	<input type="checkbox"/>	Sparklers	<input type="checkbox"/>
All objects appearing grey or yellow	<input type="checkbox"/>	Zigzag streaks of light	<input type="checkbox"/>
Distortion of all linear objects	<input type="checkbox"/>	Herringbone pattern	<input type="checkbox"/>
Dancing or moving cobwebs	<input type="checkbox"/>	Double vision	<input type="checkbox"/>
Moving black veils	<input type="checkbox"/>	Blind spot	<input type="checkbox"/>
Scintillating picket fences	<input type="checkbox"/>	None of the above (describe your own	
Silver stars	<input type="checkbox"/>		

9. Does the visual disturbance go away completely within 60 minutes?

Tick one box:

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>

10. How long does the visual disturbance last? minutes

- 11. Does the visual disturbance change (for example, get worse or change in character) within 4 minutes?**

Tick one box:

Yes ☐No ☐

- 12. Is the visual disturbance associated with headache, nausea, and/or light sensitivity immediately or within 60 minutes?**

Tick one box:

Yes ☐No ☐

- 13. With at least 2 of your headache attacks have you had temporary numbness, tingling, or both involving the lips, tongue, fingers or legs, occurring just before or during the headache?**

Tick one box:

Yes ☐No ☐

- 14. Have you had headaches accompanied by both visual disturbance and temporary numbness/tingling?**

Tick one box:

Yes ☐No ☐

- 15. Who completed this questionnaire?**

☐ You☐ Someone else...

Please state name and relationship to the person named on the front of this form:

- 16. Signature of the person completing this questionnaire:**

Date of completion:

- 17. Please return this questionnaire to us in the freepost envelope.**

THANK YOU FOR YOUR HELP!

Appendix of variables

Variable	Database	
	Field	Table
Patient-related variables		
Demographics		
Unique identifier for each patient	PatID	davesPatientDetails
Title	PatTitle	davesPatientDetails
Forename	PatForename	davesPatientDetails
Middle initials	PatInitials	davesPatientDetails
Surname	PatSurname	davesPatientDetails
Maiden name	PatMaidenName	davesPatientDetails
Date of birth	PatDOB	davesPatientDetails
Gender	PatGender	davesPatientDetails
Handedness	PatHandedness	davesPatientDetails
Marital status	PatMaritalStatus	davesPatientDetails
Ethnic code	PatEthnicCode	davesPatientDetails
CHI number	PatCHI	davesPatientDetails
Address1	PatAddress1	davesPatientDetails
Address2	PatAddress2	davesPatientDetails
Address3	PatAddress3	davesPatientDetails
City	PatCity	davesPatientDetails
District	PatDistrict	davesPatientDetails
Post code	PatPostCode	davesPatientDetails
Telephone	PatTelephone	davesPatientDetails
Email	PatEmail	davesPatientDetails
Next of kin	PatNextOfKin	davesPatientDetails
Next of kin telephone number	PatNOKPhone	davesPatientDetails

Patient-related variables (continued)*Study notifications about the patient*

Unique identifier for each notification	NotificationID	davesPatientNotification
Patient's unique identifier	NotifPatID	davesPatientNotification
Identifier for collaborator/ISD notifying the patient (from the table davesCollaborators)	NotifCollabID	davesPatientNotification
Centre the collaborator notified from (from the table davesCentres)	NotifCentreID	davesPatientNotification
GP notifying the patient (from the table davesGPs)	NotifGPID	davesPatientNotification
Date of notification	NotificationDate	davesPatientNotification
Date of first IVM diagnosis provided at notification	Notif1stDiagDate	davesPatientNotification
IVM type	IVMnotifSetType	tblIVMnotifSet
IVM quantity	IVMnotifSetQuantity	tblIVMnotifSet

Study recruitment details

Patient's GP's identifier (from the table davesGPs)	PatGPID	davesPatientDetails
Patient's main consultant's identifier (from the table davesCollaborators)	PatConsultantCollaboratorID	davesPatientDetails
Main consultant's place of work (from the table davesCentres)	PatConsultantCentreID	davesPatientDetails
Does the GP think the patient is aware of their diagnosis?	PatGPAware	davesPatientDetails
Does the consultant think the patient is aware of their diagnosis?	PatConsAware	davesPatientDetails
Overall decision about patient's awareness of diagnosis (moderated)	PatDiagAware	davesPatientDetails
Does the GP grant access to the patient's notes?	PatGPRecordsConsent	davesPatientDetails
Does the GP think SIVMS can contact the patient by post?	PatQAppropGP	davesPatientDetails
Does the consultant think SIVMS can contact the patient by post?	PatQAppropConsult	davesPatientDetails
Date of patient's completion of consent form	PatQConsentDate	davesPatientDetails
Does the patient consent to us copying their notes?	PatParticipation	davesPatientDetails
Does the patient consent to receive questionnaires?	PatQConsent	davesPatientDetails
Overall decision about postal contact with the patient	PatQOverallDecision	davesPatientDetails
Exclusion date	PatExclusionDate	davesPatientDetails
Exclusion reason	PatExcludeReason	davesPatientDetails

Patient-related variables (continued)*Hospitals visited*

Hospital's identifier (from the table davesCentres)	RegCentreID	davesPatientRegistration
Consultant's collaborator identifier (from the table davesCollaborators)	RegConsultantID	davesPatientRegistration
Does the consultant grant access to the patient's notes?	RegNotesAccess	davesPatientRegistration
Hospital's notes identification number for this patient	RegHospitalNo	davesPatientRegistration
Date of last copy letter held by SIVMS at this hospital	RegDateofLastCorrespondance	davesPatientRegistration
Hospital's imaging identification number for this patient	RegXRayNo	davesPatientRegistration

Patient's medical history

Neurological comorbidities	PatPresComorbBrain	davesPatientDetails
Systemic comorbidities	PatPresComorbSystemic	davesPatientDetails
Is there a family history of IVMs (moderated)?	PatPresIVMFamHist	davesPatientDetails
Family history details	PatIVMFamHistDetails	davesPatientDetails
Name of each drug the patient takes	DrugName	davesPatientDrug
Start date of each drug	DrugStartDate	davesPatientDrug
End date of each drug	DrugStartDate	davesPatientDrug

Patient's obstetric history

Number of children at the time of recruitment	PatChildren	davesPatientDetails
Start date of each pregnancy	PregStartDate	davesPatientPregnancy
End date of each pregnancy	PregEndDate	davesPatientPregnancy

Mode of first IVM presentation (inception)

First presentation date	PatPresentationDate	davesPatientDetails
First presentation type	PatPresentationType	davesPatientDetails

*IVM outcome events extracted from case notes**Length of follow-up*

Date of last correspondence we have from the GP notes	PatGPDateofLastCorrespondence	davesPatientDetails
Date of most recent follow-up from all sources (moderated)	PatMostRecentCommunication	davesPatientDetails

Patient-related variables (continued)		
IVM outcome events extracted from case notes (continued)		
Death		
Date of death	PatDeathDate	davesPatientDetails
Place of death	PatDeathPlace	davesPatientDetails
Cause of death	PatDeathCause	davesPatientDetails
Source of information about cause of death	PatDeathCauseSource	davesPatientDetails
Post mortem or neuropathology examination performed?	PathPMorBiopsy	tblPathology
Where the examination was performed	PathCentreID	tblPathology
Date of examination	PathDate	tblPathology
Details about each outcome event		
Date of each event	ClinEvDate	davesClinEvent
Type of event	ClinEvType	davesClinEvent
Caused by IVM/aneurysm/other	ClinEvCause	davesClinEvent
IVM causing event	ClinEvIVM	davesClinEvent
Aneurysm causing event	ClinEvAneurysm	davesClinEvent
Source of clinical event information	ClinEvSource	davesClinEvent
Type of epilepsy	EpilepsyType	tblEpilepsy
Activity of epilepsy	EpilepsyActivity	tblEpilepsy
On anticonvulsants?	EpilepsyTreatment	tblEpilepsy
Time of epilepsy?	EpilepsyTime	tblEpilepsy
Type of haemorrhage	HaemInfHaemType	tblHaemorrhagesInfarctions
Type of infarction	HaemInfInfarctionType	tblHaemorrhagesInfarctions
Radiological and/or clinical support for stroke?	HaemInfProof	tblHaemorrhagesInfarctions
Type of headache	HeadType	tblHeadaches
Headache frequency	HeadFrequency	tblHeadaches
GP-rated outcomes		
Unique identifier for GP annual questionnaire	AnnualGPID	tblAnnualGPConfirmations
Date of GP questionnaire completion	AGReplyDate	tblAnnualGPConfirmations
Modified Rankin score for each patient each year	AGModifiedRankin	tblAnnualGPConfirmations

Patient-related variables (continued)		
Patient-rated outcomes		
Unique identifier for GP (and patient) questionnaire	QAnnualGPID	davesAnnualQuest
Date of patient questionnaire completion	QcompletionDate	davesAnnualQuest
Headaches		
Has the patient had headaches this year?	QHeadaches	davesAnnualQuest
Have you had at least 5 separate attacks?	Head2	tblHeadaches
Do you have headache-free intervals of days to weeks between severe headache attacks?	Head3	tblHeadaches
Do your headache attacks usually last more than 4 hours and less than 3 days	Head4	tblHeadaches
Often pulsating	Head5a	tblHeadaches
Often on the side of the head	Head5b	tblHeadaches
Severe enough to make you stop	Head5c	tblHeadaches
Made worse by physical activity	Head5d	tblHeadaches
Nausea or vomiting	Head6a	tblHeadaches
Sensitivity to light	Head6b	tblHeadaches
Sensitivity to noise	Head6c	tblHeadaches
Visual disturbance	Head7	tblHeadaches
Silver streaks	Head8a	tblHeadaches
White lights	Head8b	tblHeadaches
Light objects appearing excessively bright	Head8c	tblHeadaches
All objects appearing grey or yellow	Head8d	tblHeadaches
Distortion of all linear objects	Head8e	tblHeadaches
Dancing or moving cobwebs	Head8f	tblHeadaches
Moving black veils	Head8g	tblHeadaches
Scintillating picket fences	Head8h	tblHeadaches
Silver stars	Head8i	tblHeadaches
Heat waves	Head8j	tblHeadaches
Flashing gold lights	Head8k	tblHeadaches
Sparklers	Head 8l	tblHeadaches
Zigzag streaks of light	Head8m	tblHeadaches

Patient-related variables (continued)

Patient-rated outcomes (continued)

Headaches (continued)

Herringbone pattern	Head8n	tblHeadaches
Double vision	Head8o	tblHeadaches
Blind spot	Head8p	tblHeadaches
None of the above	Head8Other	tblHeadaches
Does the visual disturbance go away completely within 60 minutes?	Head9	tblHeadaches
How long does the visual disturbance last?	Head10	tblHeadaches
Does the visual disturbance change (for example, get worse or change in character) within 4 minutes?	Head11	tblHeadaches
Is the visual disturbance associated with headache, nausea, and/or light sensitivity immediately or within 60 minutes?	Head12	tblHeadaches
With at least 2 of your headache attacks have you had temporary numbness, tingling, or both involving the lips, tongue, fingers or legs, occurring just before or during the headache?	Head13	tblHeadaches
Have you had headaches accompanied by both visual disturbance and temporary numbness/tingling?	Head14	tblHeadaches

Epilepsy

Has the patient had epilepsy this year?	QEpilepsy	davesAnnualQuest
Grand mal attacks	EpilepsyQ1a	tblEpilepsy
Petit mal attacks	EpilepsyQ1b	tblEpilepsy
Attacks with a trance-like state	EpilepsyQ1c	tblEpilepsy
Attacks of falling	EpilepsyQ1d	tblEpilepsy
Brief jerks of the arms and body	EpilepsyQ1e	tblEpilepsy
Some other kind of attack	EpilepsyQ1f	tblEpilepsy
Description of other kind of attack	EpilepsyQ1fDescription	tblEpilepsy
Do your attacks happen...	EpilepsyQ2	tblEpilepsy
How old were you when you had your first epileptic attack?	EpilepsyQ3	tblEpilepsy
When did you have your last attack?	EpilepsyQ4	tblEpilepsy
How many epileptic attacks have you had in the past year?	EpilepsyQ5	tblEpilepsy

Patient-related variables (continued)

Patient-rated outcomes (continued)

Barthel Index

Barthel Index (patient questionnaire identifier)	BarthelQID	davesBarthel
Bowel control	BarthelQ1	davesBarthel
Bladder control	BarthelQ2	davesBarthel
Clean teeth/brush hair/shave in last 2 days	BarthelQ3	davesBarthel
Use of toilet in past 2 weeks	BarthelQ4	davesBarthel
Eating meals in past 2 weeks	BarthelQ5	davesBarthel
Getting up in past 2 weeks	BarthelQ6	davesBarthel
Walking in past 2 weeks	BarthelQ7	davesBarthel
Dressing/undressing in past 2 weeks	BarthelQ8	davesBarthel
Climbing stairs in past 2 weeks	BarthelQ9	davesBarthel
Washing/bathing/showering in past 2 weeks	BarthelQ10	davesBarthel

Hospital Anxiety and Depression Scale (HADS)

HADS patient questionnaire identifier	HADSQID	davesHADS
Tense/wound up	HADSQ1	davesHADS
Still enjoy things as formerly	HADSQ2	davesHADS
Frightened feeling (impending doom)	HADSQ3	davesHADS
Laugh/see funny side	HADSQ4	davesHADS
Worrying thoughts	HADSQ5	davesHADS
Cheerful	HADSQ6	davesHADS
Sit at ease/relax	HADSQ7	davesHADS
Feel slowed down	HADSQ8	davesHADS
Frightened feeling (butterflies)	HADSQ9	davesHADS
Interest in appearance	HADSQ10	davesHADS
Feel restless	HADSQ11	davesHADS
Look forward with enjoyment	HADSQ12	davesHADS
Sudden panic	HADSQ13	davesHADS
Enjoy book/radio/TV	HADSQ14	davesHADS

Patient-related variables (continued)		
Patient-rated outcomes (continued)		
Modified Rankin		
Modified Rankin patient questionnaire identifier	MRankinQID	davesMRankin
Patient-rated question	MRankinQ1	davesMRankin
Short Form-36 (SF-36)		
SF-36 patient questionnaire identifier	SF36QID	davesSF36
General health now	SF36Q1	davesSF36
Change in health	SF36Q2	davesSF36
Vigorous activities limited by health	SF36Q3a	davesSF36
Moderate activities limited by health	SF36Q3b	davesSF36
Lifting/carrying groceries limited by health	SF36Q3c	davesSF36
Climbing several flights of stairs limited by health	SF36Q3d	davesSF36
Climbing 1 flight of stairs limited by health	SF36Q3e	davesSF36
Bending/kneeling/stooping limited by health	SF36Q3f	davesSF36
Walking > 1 mile limited by health	SF36Q3g	davesSF36
Walking several blocks limited by health	SF36Q3h	davesSF36
Walking 1 block limited by health	SF36Q3i	davesSF36
Bathing/dressing self limited by health	SF36Q3j	davesSF36
Cut time on work/other activities due to health in past 4 weeks	SF36Q4a	davesSF36
Accomplished less work/other activities due to health in past 4 weeks	SF36Q4b	davesSF36
Limited type of work/other activities due to health in past 4 weeks	SF36Q4c	davesSF36
Had difficulty with work/other activities due to health in past 4 weeks	SF36Q4d	davesSF36
Cut time on work/other activities due to emotional problems in past 4 weeks	SF36Q5a	davesSF36
Accomplished less than would wish due to emotional problems in past 4 weeks	SF36Q5b	davesSF36
Less care over work/other activities due to emotional problems in past 4 weeks	SF36Q5c	davesSF36
Social activities impacted by health/emotional problems in past 4 weeks (degree)	SF36Q6	davesSF36

Patient-related variables (continued)		
Patient-rated outcomes (continued)		
SF-36 (continued)		
Bodily pain during past 4 weeks	SF36Q7	davesSF36
Normal work impacted by pain in past 4 weeks	SF36Q8	davesSF36
Full of pep in past 4 weeks	SF36Q9a	davesSF36
Very nervous in past 4 weeks	SF36Q9b	davesSF36
Down in dumps in past 4 weeks	SF36Q9c	davesSF36
Calm and peaceful in past 4 weeks	SF36Q9d	davesSF36
Lots of energy in past 4 weeks	SF36Q9e	davesSF36
Downhearted and blue in past 4 weeks	SF36Q9f	davesSF36
Worn out in past 4 weeks	SF36Q9g	davesSF36
Happy in past 4 weeks	SF36Q9h	davesSF36
Tired in past 4 weeks	SF36Q9i	davesSF36
Social activities impacted by health/emotional problems in past 4 weeks (duration)	SF36Q9j	davesSF36
Get sick easier than other people	SF36Q10a	davesSF36
Healthy as anyone	SF36Q10b	davesSF36
Expect health to worsen	SF36Q10c	davesSF36
Health is excellent	SF36Q10d	davesSF36
Hereditary haemorrhagic telangiectasia (HHT) annual screening questions		
Epistaxis	HHTNoseBleed	davesHHT
Age epistaxis started	HHTNBldStartAge	davesHHT
Frequency of epistaxis	HHTNBldFreq	davesHHT
Telangiectasia	HHTRedSpots	davesHHT
Number of telangiectasia	HHTRedSpotNo	davesHHT
Location of telangiectasia	HHTRedSpotLoc	davesHHT
IVM-related variables		
Patient details		
Date of patient's first-ever IVM diagnosis (moderated)	PatDiagnosisDate	davesPatientDetails
IVM multiplicity for this patient	PatIVMCode	davesPatientDetails

IVM-related variables (continued)*General characteristics of each IVM*

Type of IVM	IVMType	davesIVM
Date of earliest definite diagnosis of this IVM	IVM1stDiagDate	davesIVM
Side of brain	IVMSide	davesIVM
Brain area	IVMBrainArea	davesIVM
Location in brain area	IVMLocation	davesIVM
Eloquence of brain area	IVMEloquence	davesIVM
Spetzler Martin grade (brain AVMs only)	IVMSpetzlerMartin	davesIVM
Borden grade (dural AVMs only)	DAVFBordenGrade	tbiDAVF
Cognard grade (dural AVMs only)	DAVFCognard Grade	tbiDAVF

Additional general characteristics of each IVM from every type of brain imaging

Degree of certainty about diagnosis	RadDegreeOfCertainty RadDegreeOfCertainty PIIVMCertainty	davesRadAng davesRadCTMR tbiPathologyIVMs
IVM size (x dimension)	RadIVMsizeX RadAVMsizeX	davesRadAng davesRadCTMR
IVM size (y dimension)	RadIVMsizeY RadAVMsizeY	davesRadAng davesRadCTMR
IVM size (z dimension)	RadIVMsizeZ RadAVMsizeZ	davesRadAng davesRadCTMR
Are there any associated aneurysms on the scan?	ScanAneurysms	davesScan

Catheter angiogram data

Is the angiogram normal?	ScanAngioNormal	davesScan
Did superselective angiography reveal further information?	ScanSSAExtraInfo	davesScan
Avascular mass on angiography?	RadAvascularMass	davesRadAng
Degree of arterial tortuosity	RadArterialTortuosity	davesRadAng
Arterial angiopathy	RadArterialAngiopathy	davesRadAng
Angiogenesis	RadAngiogenesis	davesRadAng
Collateral vessels	RadAngioCollaterals	davesRadAng
Origin of collateral supply	RadAngioCollatSupply	davesRadAng
Related to a dural sinus?	RadAngioSinusRelatedTo	davesRadAng
Side of the sinus	RadAngioSide	davesRadAng
State of the sinus	RadAngioSinusState	davesRadAng

IVM-related variables (continued)*Catheter angiogram data (continued)*

Unique identifier for each arterial feeder	ArtFeederID	davesArtFeeders
Scan the feeder was identified on	ArtFeedScanID	davesArtFeeders
IVM the feeder is associated with	ArtFeedIVMID	davesArtFeeders
Type of feeder	ArtFeedType	davesArtFeeders
Side of the feeder	ArtFeedSide	davesArtFeeders
Type of feeding branch	ArtFeedBranch	davesArtFeeders
Quantity of feeders from each branch	ArtFeedQuantity	davesArtFeeders
Number of draining veins	AVMNidusCompts	tblAVM
Dominant venous trunk	AVMDominantTrunk	tblAVM
Destination of each draining vein	DVVein	tblDrainingVeins
Side of each draining vein	DVSide	tblDrainingVeins
Direction of flow (dural AVMs only)	DVFlowDirection	tblDrainingVeins
Pattern of venous drainage	AVMDrainPattern	tblAVM
Venous varices	AVMVenousVarices DAVFVenousVarices	tblAVM tblDAVF
Venous ectasia	AVMVenousEctasia DAVFVenousEctasia	TblAVM tblDAVF
Venous stenosis	AVMVenousStenosis	tblAVM
Location of venous stenosis	AVMVenousStenosisLoc	tblAVM
Type of brain AVM nidus border	AVMNidusBorder	tblAVM
Discernible fistula in brain AVM nidus	AVMNidusFistula	tblAVM

CT/MRI data

Mass effect on the scan	RadMassEffect	davesRadCTMR
Hydrocephalus on the scan	RadHydrocephalus	davesRadCTMR
Oedema related to IVM	RadOedema	davesRadCTMR
Vessel calcification on CT	RadCTVesselCalcification	davesRadCTMR
Calcification from old haemorrhage on CT	RadCTOldHaemCalc	davesRadCTMR
Gliosis on MRI	RadMRIGliosis	davesRadCTMR
Evidence of prior haemorrhage on MRI	RadMRIOldHaemEvidence	davesRadCTMR
Acute haemorrhage	RadAcuteHaem	DavesRadCTMR

IVM-related variables (continued)*CT/MRI data (continued)*

Type of haemorrhage	RadNewHaemType	davesRadCTMR
Brain area of haemorrhage	RadNewHaemArea	davesRadCTMR
Side of haemorrhage	RadAcuteHaemSide	davesRadCTMR
Low density without mass effect (CT)	RadLowDensity	davesRadCTMR
Cerebral infarction (MRI)	RadCerebralInfarction	davesRadCTMR
Cerebral infarction location (MRI)	RadCerebralInfarctionLoc	davesRadCTMR
Cerebral infarction side (MRI)	RadCerebralInfarctionLocSide	davesRadCTMR
Dilation of adjacent dural sinus	RadDilation	davesRadCTMR
Thrombosis of adjacent dural sinus	RadThrombosis	davesRadCTMR
Perinidal contrast enhancement on MRI	RadMRIPerinidalEnhance	davesRadCTMR
Signal characteristics on MRI (CMs only)	RadSignalCharsCM	davesRadCTMR

Variables related to associated aneurysm(s)

Aneurysm unique identifier (identified on brain imaging)	AneurID	davesAneurysm
Aneurysm unique identifier (identified by pathology)	PA_AneurysmID	tbiPathologyAneurysms
Patient ID	AneurPatID	davesAneurysm
Location	AneurLocation	davesAneurysm
Artery	AneurArtery	davesAneurysm
Side	AneurSide	davesAneurysm
Morphology	RadAneurMorph	davesRanAneur
Aneurysm diameter	RadAneurLuminDiam	davesRanAneur

Interventions

Aneurysm / IVM identifier	IntervIVMID IntervAneurysmID	tbiInterventions
Type of intervention	IntervType	tbiInterventions
Date of intervention	IntervDate	tbiInterventions
Did they receive the intervention?	IntervTreated	tbiInterventions